KU Leuven
Group Biomedical Sciences
Faculty of Pharmaceutical and Pharmacological Sciences
Clinical Pharmacology and Pharmacotherapy

Legal framework applicable to access to biobanks

Michiel VERLINDEN

Jury:

Promotor:	Prof. Dr. Isabelle Huys
Co-promotor:	Prof. Dr. Herman Nys and prof. dr. Nadine Ectors
Chair:	Prof. Dr. Ann Gils
Jury Members:	Prof. Dr. Mette Hartlev
	Prof. Dr. Gerhard Zielhuis
	Prof. Dr. Katelijne De Nys
	Prof. Dr. Stefaan Callens

Leuven, 20.03.2015

Doctoral thesis in Pharmaceutical Sciences

Public defence:

Friday March 20th 2015, 10h00

Auditorium
Arenberg Kasteel
Kasteelpark Arenberg 1
3001 Heverlee

Promotor: Prof. Dr. Isabelle Huys
Co-promotor: Prof. Dr. Herman Nys and prof. dr. Nadine Ectors

Clinical Pharmacology and Pharmacotherapy
Department of Pharmaceutical and Pharmacological Sciences
KU Leuven
Herestraat 49, O&N2, PB 521
B-3000 Leuven

Acknowledgement

This PhD could not have been realized without the support of a number of organizations and persons.

I wish to acknowledge the Agency for Innovation by Science and Technology in Flanders (IWT). This PhD project was funded via the “Strategic Basic Research” Programme of IWT.

I wish to acknowledge the Faculty of Pharmaceutical and Pharmacological Sciences (KU Leuven) and the Department of Biomedical Sciences (KU Leuven) for the opportunity to conduct this interdisciplinary PhD project.

I wish to acknowledge the FWO (Fonds voor Wetenschappelijk Onderzoek) for providing me with a Travel Grant for a Long Stay Abroad for my first research stay at the University of Copenhagen.

I wish to acknowledge the KU Leuven and in particular the Research Coordination Office, for funding my research stays at the University of Copenhagen under the Junior Mobility Programme.

I wish to acknowledge the Faculty of Law of the University of Copenhagen for hosting me as visiting researcher during two research stays at the faculty. I wish to thank in particular prof. Mette Hartlev, prof. Jens Schovsbo and prof. Timo Minssen for their guidance and support.

Thanks to Prof. Ann Gils and the members of the thesis advisory comittee, Prof. Katelijne De Nys and Prof. Stefaan Callens to follow up my doctorate through the years and for their constructive review of this manuscript. Many thanks also to the external members of the jury, Prof. Mette Hartlev and Prof. Gerhard Zielhuis, for their valuable comments and suggestions.

Some of the studies were only possible through the help and input of others. Thank you Prof. Inger Stensaker, Prof. Ingeborg Kleppe, Prof. Klaus Hoeyer and Prof. Pascal Borry for your valuable suggestions in designing the qualitative study in Chapter 2. Thank you Prof. Timo Minssen for your critical suggestions and support in drafting Chapter 4.

I wish to thank the informants that participated in the qualitative study in Chapter 2.

Dankwoord

Ik wens nog een aantal mensen te bedanken voor hun hulp om dit doctoraatsproject tot een goed einde te kunnen brengen.

Vooreerst mijn promotoren voor hun uitstekende ondersteuning tijdens de afgelopen 4 jaar. Hun praktisch ervaring en expertise als deskundigen was van onmisbaar waarde voor dit doctoraat. Nadine, veel dank voor het delen van je uitgebreide praktisch ervaring en expertise inzake biobanken en om mij de mogelijkheid te bieden deel te nemen aan de ESBB conferenties. Herman, dat jouw deur altijd openstond voor mij, de vele goede commentaar die ik van je kreeg, en dat je mij de mogelijkheid bood om een deel van mijn doctoraatsproject uit te voeren in het Interfacultaire Centrum voor Biomedische Ethiek en Recht, het heeft allemaal veel voor mij betekend en is de kwaliteit van mijn doctoraat zeer ten goede gekomen. En Isabelle, ik wens jou in het bijzonder te bedanken, voor je intellectuele, praktische en niet in het minst je morele steun. Je immense toewijding en geduld bij het begeleiden van dit doctoraatsproject hebben voor mij echt het verschil gemaakt.

Ik wens ook mijn collega's te bedanken in het Onderzoekscentrum voor Klinische Farmacologie en Farmacotherapie, het Interfacultaire Centrum voor Biomedische Ethiek en Recht en het Centrum voor Intellectuele Rechten. Bij jullie kon ik terecht voor een goede babbel en vele kleine praktische vragen. Ik wens Hilde in het bijzonder te bedanken voor alle interessante gesprekken die we hadden de afgelopen vier jaar en die mij in de laatste fasen van dit project telkens weer moed en vertrouwen gaven.

Tenslotte wens ik mijn familie en vrienden te bedanken voor hun praktische en morele steun tijdens dit doctoraatsproject. Pascale, voor het nauwgezet nalezen van de tekst van het doctoraat. Tineke, Stefan, Emma en Rosa wil ik bedanken voor jullie interesse, de grafische hulp, en in het bijzonder om jullie goede zorgen tijdens de laatste loodjes van mijn doctoraat. Mijn ouders, voor de vele kansen die jullie mij geboden hebben en voor jullie onvoorwaardelijke vertrouwen en geduld tijdens mijn vele "studieprojecten". Mijn zus, Niek, omdat ik steeds bij je terecht kon wanneer ik even stoom moest aflaten of een doordachte tweede opinie nodig had. Er bestaan, ten slotte, geen woorden om uit te drukken hoe dankbaar ik Josefine en Jacob ben. Zonder jullie had dit doctoraat nooit bestaan.

Table of Contents

Definitions

The term '**Access Arrangements**' can be defined as "guidelines, best practices, opinions, policies, agreements, etc. containing rules on access to and use of HBM and data collections stored within biobanks'.

The term '**Basic data**' is defined as 'data that has not been subjected to analysis or any other processing, except for the purpose of storing the data or providing it to an applicant'.

The term '**Basic HBMs**' can be defined as 'HBMs that have not been subjected to processing or any other manipulation, except for the purpose of storing the HBM or providing it to an applicant*'*. '

The term '**Biobank'** refers to 'a structure that obtains, processes, stores and provides human bodily material and possible also associated data and this (only) for scientific research purposes, excluding research that implies medical applications to humans" (art. 2, 27° of the Belgian Act on HBM of 19 December 2008).

The term '**Biobank Network**' refers to 'a group of institutions who freely assume the commitment to collaborate in the domain of biobanking and who (often) share the same procedures and quality policies, and who are (or might be) helped by a central hub for coordination in terms of service*'* (1).

The term '**Biobank Initiatives'** covers biobanks, biobank networks as well as organizations.

The term '**Custodianships**' can be defined as the 'caretaking responsibility for HBM and data that starts at the planning of a biobank initiative, prior to the collection, and continues through research use to final dissemination of research results' (a slight adapted version of the definition used by R. Yassin *et al.* (2) and the National Cancer Institute (3)).

The term '**Epidemiology**" could be described as "*the study of the incidence, extent and causes of occurrences of disease epidemics. Such a study can lead to mitigation of the effects of future outbreaks of a disease, as well as the prediction of its likely extent*."

The term '**Organizations**' refers to 'organizations and associations not directly involved in the management of a biobank or biobank network, but active in the development of guidelines, policies or best practices pertaining to access to HBMs or data or both'.

The term '**Ownerships**' can be defined as 'The ultimate and exclusive right conferred by a lawful claim or title, and subject to certain restrictions to enjoy, occupy, possess, rent, sell, use, give away, or even destroy an item of property'[1].

The term '**Residual HBM**' or '**Leftover HBM**' refers to "the part of HBM that was removed for diagnostic purposes or treatment of the donor and that – after a sufficient and relevant part has been stored to conduct, refine or complete the diagnosis or treatment of the donor on the basis of new scientific data – has become redundant for such purposes and therefore could be destroyed" (art.2, 33° of the Belgian Act on HBM).

[1] http://www.businessdictionary.com/definition/ownership.html

The term '**Personal Data**' refers to "any information relating to a person that can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural, or social identity" (art. 1, § 1 Belgian Privacy Act).

The term '**Personalised medicine**' refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention (Horizon 2020)

The term '**Researcher**' refers both to researchers from the academic sector (e.g., university or research institutes), the public sector (e.g., public institutions conducting research such as ministries, government agencies and public hospitals) and the private sector (e.g., private institutions, such as industrial or commercial businesses)(4).

Lists

1 List of abbreviations

ATMP	Advanced Therapy Medicinal Product
BBMRI	Biobanks and Biomolecular Resources and Research Infrastructure
CMI	Centre for Medical Innovation
ECRIN	European Clinical Research Infrastructure Network
EPC	European Patent Convention
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
FDA	Food and Drug Administration
HBM	Human Biological Material
IPR	Intellectual Property Rights
ISBER	International Society for Biological and Environmental Repositories
MA	Marketing Authorization
MTA	Material Transfer Agreement
NCI	National Cancer Institute
OECI	Organisation of European Cancer Institutes
PI	Principle Investigator
P^3G	the Public Population Project in Genomics and Society
OECD	Organization for Economic Cooperation and Development
R&D	Research and Development
REC	Research Ethics Committee
SOP	Standard Operating Procedure
UNESCO	The United Nations Educational, Scientific and Cultural Organization

2 List of figures

3 List of tables

Part 1: General introduction and scope

1 General introduction

1.1 Importance of biobanking for biomedical research

Already in 2009, Time Magazine listed biobanking as one of the Top 10 ideas that change the world right now(5). The European Commission recognized the sound governance of biobanks as one of the most important challenges for the European innovation system (6). The European Strategy Forum on Research Infrastructures (ESFRI) identified biobanks as one of the main priority research infrastructures for the European Research Area (ERA) for the next 10 to 20 years(7,8). The 'Biobanking and Biomolecular resources Research Infrastructure' (BBMRI) was one of the first projects under the European Research Infrastructure Preparatory Phase of the ESFRI (9,10).

Millions of human biological material (HBM) and associated data are collected each year for a variety of purposes. These purposes include, for instance, basic research studies, clinical trials and epidemiological studies(11,12).

Art. 2, 27° of 19 December 2008 of the Belgian Act on HBM defines a biobank as: "'a structure that obtains, processes, stores and provides human bodily material and possible also associated data and this (only) for scientific research purposes, excluding research that implies medical applications to humans." The collection and storage of HBM in so-called 'biobanks' is not a new phenomenon. It has been done for more than 100 years in different ways and for different purposes(13). The rise of new scientific disciplines, such as genomics, proteomics and bioinformatics, has considerably increased the demand for the systematic collection of large amounts of high quality HBM and data (9,10), and new sequencing technologies. The use and access to HBMs and data stored in biobanks, has therefore become a crucial component in many biomedical research projects (14–17).

Collections of HBM and data vary in scope, form and scale, according to the type of HBM and data that is collected and the different purposes for which they are used (18). The scale ranges from small collections in hospital or university departments to the storage of large amounts of HBM in specifically designed and well-equipped facilities (13,19).

Different aspects determine the value of a biobank. The quality of the samples and associated data and the ability to link the samples with donor information are two of these factors(20).

In the realm of translational research, biobanks will take a central place in the R&D process of medicines. Biobanks can provide a crucial platform for international and interdisciplinary cooperation and act "as key drivers for next generation biomarker (diagnostics) research and drug discovery"(21). Good functioning models for access to HBM and data are crucial.

The legal framework that determines access to biobanks often remains unclear. The absence of a defined set of applicable rules creates legal uncertainty for biobanks and applicants. The PhD project investigated the hopes and concerns of the different stakeholders – focusing on custodians of biobanks and applicants – in biobanking. It mapped and characterised the (existing) heterogeneous legal framework applicable to biobanks and formulated recommendations for the development of a transparent, feasible and encouraging legal framework suitable for access to biobanks.

1.2 Different types of human biological material and associated data collected

1.2.1 Different types of HBM

Many different types of HBM are collected and stored in biobanks and used in biomedical research[2]. Biobanks collect solid human tissue, such as skin, brain, bone or tumour-related tissue. Another type of HBM and data stored in biobanks are human liquids, such as blood, urine, saliva and cerebrospinal fluids. Some biobanks also collect and store isolated human genetic material, such as DNA, RNA and specific types of genetic information contained in blood, tissues, serum, plasma, cells and cell lines. A fourth type of HBM is isolated cells, such as stem cells, T and B lymphocyte cells and liver cells.

A distinction is often made between common and rare HBM. Common HBM, such as blood, is collected and stored on a regular basis and is therefore available in large amounts. Rare HBM, such as brain tissue or HBM relating to a rare pathology is only available in limited amounts. That is why some argue that access to and use of rare HBM should be handled with more caution(22).

1.2.2 Degree of identification of HBM

The degree of identification of HBM stored in a biobank may vary.

The first option is that the origin of the HBM cannot be traced back to the original donor. In this case the HBM is stored alone or in combination with limited associated data, such as age, sex and pathology. It does not allow, with reasonable efforts, the identification of the patient(23). Since the HBM cannot be traced back, there is no possibility to obtain additional information about the patient that donated the HBM. This is called anonymous or anonymised HBM.

The second option is that the origin of the HBM can be traced back to the donor on the basis of a code. Only the person that holds the identification code, can link the donated HBM to the identity and the personal information of the donor. The identification code is not accessible to researchers that use the HBM. This is called coded HBM.

The last option is that the researcher has direct access to the code that allows the identification of the donor of HBM used in a research project. This is called identifiable HBM(19,24).

[2] The distinction between the different types of HBM is not absolute, since some HBM can be considered as being several types of HBM. For instance, blood is a liquid tissue that contains cells, that contains DNA. We merely wanted to highlight that biobanks collect and store many different types of HBM.

1.2.3 Different types of data associated with HBM

The value of HBM for medical and scientific research depends to a large extent on the availability of sufficient personal information about the donor and his pathology. This personal information may include demographic information – such as age and gender – as well as information about lifestyle, environmental factors, family history, the medical history of the patient from whom HBM was collected, medical interventions (including medicine), follow-up data (such as course of disease) (9,20,25).

1.3 Different reasons to use human biological material and associated data for research purposes

HBM and associated data can be used for diagnostic, therapeutic of research purposes. This PhD focuses on the use of HBM and data for research purposes.

HBM and associated data are particularly important for translational research. Translational research can be considered as the essential link between basic and clinical research. It focuses on the use of data from pre-clinical studies in clinical research. This type of research tries to translate promising findings in the laboratory to an application for the patients. The development of personalized treatments or medicine is an example of such translational research.

Biobanks can provide access to HBM and data for research aiming to identify new biomarkers. In doing so, they can play a crucial role in translational research. Biomarkers are specific cells, molecules, genes, gene products, enzymes or hormones that can be measured in an objective and quantitative manner. They can be used as an indicator of normal biological processes and pathological processes. Biomarkers provide support for the prediction, prevention, diagnosis and treatment of many existing diseases (26–29).

HBM and data stored in a biobank can contribute to research on the identification of new molecular targets for drugs (26–28). They are also used to confirm results in humans clinical applications that were successfully tested in animal models(9,25). Well-characterized HBM are particularly interesting for research into new drug targets, since they mimic more accurately what happens in the human body.

HBM can also be used to test a new drug before going into a clinical trial. This makes it possible to obtain more information about the human pathology. It can accelerate drug development, since it allows focusing more in the development and testing of a new drug. This should lead to less negative results in later phases of drug development (9).

New techniques have made it possible to study in more detail the genetic material, DNA, RNA and proteins extracted from HBM such as tissues, cells and blood. This allows research on factors that may impact disease processes. Researchers try to better understand diseases by examining HBM of people both with and without the same disease. They compare their findings with genetic mutations as a result of environment and lifestyle of the patient (9).

Combining HBM with "up to date" associated data from the donors is crucial to increase the chances of success of the research and to obtain significant results (9,25).

HBM and associated data are also very often used for cohort-based research or epidemiological research. Such research is conducted on a sample of the population of a particular country or part of a country. The participants of such research are randomly enrolled via population registries(30). After enrolment, HBM – such as blood or isolated DNA – and associated data are collected from the participants(9). Additional data is obtained via health questionnaires, physical measurements, psychological tests, etc. During the course of the study the participants are re-contacted on a regular basis – for instance every five years – to obtain follow-up HBM and data. This makes it possible to study a wide range of different health risks over a longer period of time(31).

Epidemiological research is primarily devoted to the interaction between "*the genetic background, lifestyle, environmental and others determinants that may influence the incidence, development and treatment response for various diseases*" (31). Since patients are followed during a longer period of time, one can assess the exposures to those determinants prior to the development of a disease(32). Epidemiological research does not focus on the diagnosis and treatment of a particular disease(27,28). Examples of large-scale epidemiological studies are the UK Biobank, the HUNT study in Norway, the LifeGene Study in Sweden and the LifeLines study in the Netherlands(32).

1.4 Biobanks

Although collections of HBM and data have existed for more than a century, the term 'biobank' is still relatively new. The term appeared for the first time in scientific literature in 1996, but it only became commonly used after 2000. The term 'biobank' is used to refer to various types of collections of HBM and data that are stored for different purposes(33,34). Some alternative terminology that are still used – mostly outside Europe – are 'biological specimen banks', 'bioresources', 'biological resources' and 'biorepositories'.

1.4.1 Legal definition of a biobank

In order to acquire a deeper understanding of the term 'biobank', we looked into different definitions in international normative documents and legislation of a number of European countries[3]. The definition of a biobank in principle has an influence on the determination of the applicable rules. However, some postulate that the applicable legislation should be determined on the basis of the different activities pursued rather than on the definition of a 'biobank' as such(35).

1.4.1.1 Overview of different definitions

The international organization 'Public Population Project in Genomics and Society' (**P³G**) defines biobanks as "*an organized collection of human biological material and associated information stored for one or more research purposes*(4)."

[3] The overview was created on the basis of definitions enlisted on the website of the EU funded research project PRIVILEGED (http://www.privileged.group.shef.ac.uk/projstages/stage1/introduction/biobank-defs/) and an overview of the Nordic Committee on Bioethics(38) and supplemented and updated with additional definitions in national legislations.

The Organization for Economic Co-operation and Development (**OECD**) defines 'human biobanks and genetic research databases' (HBGRD) as "*structured resources that can be used for the purpose of genetic research and which include: (a) human biological materials and/or information generated from the analysis of the same; and (b) extensive associated information*(36)." This definition is limited to collections of HBM and data that can be used for genetic research purposes.

A paper describing the preparatory work to develop **BBMRI-ERIC**[4] defines a 'biobank' as "*large collections of well-documented, up-to-date epidemiological, clinical and biological information and accompanying material from large numbers of patients and healthy persons* (10)."

The statutes of the BBMRI-ERIC defines 'Biobanks (and Biomolecular Resources Centres)' as "*collections, repositories and distribution centres of all types of human biological samples, such as blood, tissues, cells or DNA and/or related data such as associated clinical and research data, as well as biomolecular resources, including model- and micro-organisms that might contribute to the understanding of the physiology and diseases of humans* (37)*."* This definition applies to all kind of collections of HBM and associated data, irrespective of whether such collections are used for research purpose or for therapeutic of diagnostic purposes. The definition furthermore includes biomolecular resources such as model- and microorganisms.

Article 2, 27° of the **Belgian** Act of 19 December 2008 on HBM[5] – as modified by an Act of 15 March 2013 containing diverse health provisions – defines a 'biobank' as a "*structures that obtains, processes, stores and provides human bodily material and possible also associated data and this (only) for scientific research purposes, excluding research that implies medical applications to humans*[6]." The Belgian Act of 19 December 2008 defines 3 additional types of infrastructures that collect HBM and data for therapeutic use of HBM and data. These are the bank for human bodily material, the intermediate structure for human bodily material and the production establishment. Distinct legal rules are applicable to the four different types of infrastructures.

The Report no. 1414/2002[7] of the **Danish** 'Biobanking Working Group' defined a biobank as "*a structured collection of human biological material available according to specific criteria and where the information contained in the samples can be traced to identifiable persons*" (38). A collection is not considered as a biobank when samples in the collection cannot be traced directly or indirectly – for example via an encryption key – back to identifiable persons (39).

[4] The Biobanking and Biomolecular resources Research Infrastructure-European Research infrastructure consortium
[5] The Belgian Act of 19 December 2008 on the procurement and use of human bodily material
[6] Free translation of future article 2, 27°: "de structuur die, met het oog op wetenschappelijk onderzoek met uitsluiting van onderzoek met geneeskundige toepassing op de mens, menselijk lichaamsmateriaal verkrijgt, in voorkomend geval bewerkt, bewaart en ter beschikking stelt, evenals desgevallend de daaraan gekoppelde gegevens die betrekking hebben op het menselijk lichaamsmateriaal en de donor";
[7] The "Report on biobanks – proposal for a legal regulation of biobanks within the health field" (Report no. 1414/2002)

The **Norwegian** legislation distinguishes between treatment and diagnostic biobanks, on the one hand, and research biobanks, on the other hand. A 'treatment or diagnostic biobank' is defined as "*a collection of HBM contributed for the purpose of medical examination, diagnosis and treatment*." A 'research biobank' is defined as a "*collection of HBM that is used or is to be used for research purposes*." The Norwegian legislation does not seem to refer explicitly to the collection of associated data in combination with the HBM(38).

The **Portuguese** legislation[8] defines a 'biobank' in quite an elaborate manner as "*any depository of biological samples and related derivatives, with or without a pre-defined period of storage, based on prospective collection or made up of previously collected material, obtained for health care purposes, public health monitoring programs, or for research, and that includes identified, identifiable, anonymized or anonymous samples*." The definition includes many different types of biobanks.

The **Swedish** Act on Biobanks (SF 2002:297) defines a 'biobank' as "*biological material from one or several human beings collected and stored indefinitely or for a specified time and whose origin can be traced to the human or humans from whom it originates*[9]."

In 2004, the opinion on 'Biobanks for Research' of the **German** National Ethics Council defined 'biobanks' as "*collections of samples of human bodily substances that are or can be associated with personal data and information on their donors*." With bodily substances is meant, amongst others, cells, tissue, blood, or DNA as the physical medium of genetic information. The definition refers to the twofold character of biobanks, as collections of both samples and data.

The **Estonian** Human Genes Research Act of 2000 defines 'gene banks' as "*a database established and maintained by the chief processor consisting of tissue samples, descriptions of DNA, descriptions of state of health, genealogies, genetic data and data enabling the identification of gene donors."*

The **Icelandic** Act on Biobanks No. 110/2000 defines a 'biobank' as "*a collection of biological samples, which are permanently preserved*." Collections of HBM stored for less than 5 years are not considered biobanks[10]. The Icelandic legislation furthermore makes a distinction between research biobanks, that preserve research samples, or clinical biobanks, that preserve clinical samples(38).

Report n° 77[11] of the **French** National Consultative Ethics Committee on Health and Life Sciences remarks that '*the word biobank today seems to allude to some form of deposit of property with a market value*.' The report instead uses the term 'biolibraries' as "*an assembly of biological materials potentially vectors of genetic information (i.e. possessing cells or directly extracted genetic material). Files, possibly computerised, are associated to this assembly of biological material, and are composed of the data, which is essential for it to be exploited (origin of donors, genealogy, clinical and biological data). Samples may have been provided by healthy volunteers or the sick for clinical purposes,*

[8] Law no. 12/2005, 26th of January, article 19, no 1
[9] http://www.biobanks.se/biobank.htm
[10] http://www.privileged.group.shef.ac.uk/projstages/stage1/introduction/biobank-defs/
[11] Report n° 077 of the French National Consultative Ethics Committee on Health and Life Sciences, entitled "Ethical issues raised by collections of biological material and associated information data: "biobanks", "biolibraries"" of 20 March 2003

research projects, or judicial activities. To the above must now be added embryonic samples for the creation of stem cell banks." This definition of 'biolibraries' includes many different types of collections of HBM and data and explicitly refers to the potential use of HBM and data for judicial activities.

1.4.1.2 Comparison of different definitions

The comparison of the different legal definitions of biobanks reveals that some differences in the wording of the term "biobank" could stem from different views on the concept of biobanks. A little more than half of the definitions limits the scope of biobanks to collections used for research purposes. The other half of the definitions includes the use of HBM and data for therapeutic and diagnostic purposes. The definitions of a biobank in Sweden, Estonia and Denmark explicitly provide that it only relates to identifiable HBM, while the legal definition of biobanks in Portugal and Belgium relates both to identifiable and non-identifiable HBM. The Icelandic definition only considers a collection of HBM (and data) as a biobank, when the HBM and data has been collected for a certain period of time (more than 5 years).

Other differences in wording seem to be merely different (practical) interpretations of the same concept of biobanks. The majority of the definitions stipulates that biobanks are collections that consist both of HBM and data, while a few definitions only (explicitly) refer to HBM and not to data. The majority of the definitions specify that biobanks concern collections of biological material of human origin, while some definitions do not clearly specify the type of biological material. The definition contained in the statutes of the BBMRI-ERIC also makes reference to biomolecular resources. In this PhD we use the legal definition of a biobank as provided in the Belgian Act on HBM.

1.4.2 Different types of biobanks

The concept of biobanks represents a large variety of collections of HBM and data stored and used for different purposes. An important distinction between different types of biobanks is based on their function or activity: (1) population-based prospective biobanks and (2) disease-oriented biobanks. The distinction between those types of biobanks is, however, not absolute, since one could use other criteria to distinguish different types of biobanks.

1.4.2.1 Population-based (prospective) biobanks

The Recommendation Rec (2006)4 of the Council of Europe defines a "*population biobank*" as a collection of HBM that*: (i) has a population basis; (ii) is established, or has been converted, to supply biological materials or data derived therefrom for multiple future research projects; (iii) contains biological materials and associated personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated; (iv) receives and supplies materials in an organised manner"* (40).

A population-based biobank (prospectively) stores large amounts of HBM (and data) of well-defined phenotypes over a long period of time. It is used to identify and characterize the health status of large groups of individuals (3). HBM (and data) stored in such population-based biobanks is often collected from health volunteers rather than from patients. Such biobank is not necessarily located in a hospital (4). Examples of population-based biobanks are, the UK Biobank, the Norwegian Mother and Child

Cohort Study and the Hunt Study in Norway, CARTaGENE in Canada, the Estonian Biobank, the LifeLines Cohort & Biobank initiative in the Netherlands, Genome Database of Latvian Population and LifeGene in Sweden (41).

Population-based biobanks can be further divided into three subtypes(9). A first subtype is a biobank consisting of a longitudinal collection of HBM and data obtained from a general population. The HBM and data was collected from individuals that were selected by means of random sampling. The type of HBM that is collected most often in this context is blood and isolated DNA. Usually HBM and associated data is collected at the beginning of a study. The collection is then completed and updated at specific times during the follow-up of the study. This approach has several advantages. Since one starts from a general population, one can study the natural frequency of the occurrence of a disease. Special attention is given to genetic variations and environmental risks. A second advantage is the ability to study the biomarkers that can predict the onset of a particular disease in a healthy individual. A disadvantage of this method is the long duration required to set up such kind of study. A sufficient number of individuals have to be affected by a particular disease before one can study the disease. A genome scan, required to investigate genetic polymorphism associated with a particular disease, for example, necessitates DNA of at least 10,000 individuals. This clearly shows how international cooperation that combines the stored HBM and data of different biobanks is important to accelerate such research (9,25,31).

An example of the first subtype is the UK Biobank[12] that aims to collect HBM and data of more than 500.000 donors. The donors are selected to represent the ethnic diversity within the United Kingdom. They are recruited between the age of 40 and 69 years in order to make sure that the group of donors represent most of the different disease phenotypes(42,43). The aim of the UK Biobank is to study the influence of inherited genetic variations, environmental factors and the life style of the donors on the risk of developing particular diseases, such as cancer, heart disease, stroke, diabetes, arthritis, osteoporosis, eye disease, depression, and certain forms of dementia(31).

A second subtype comprises biobanks that are focused on a specific isolated population. Such biobanks are for instance used to study specific ethnic groups for which one has sufficient information regarding the family history over several generations(9).

A third subtype is biobanks based on HBM and data of twins (so-called “twin registry biobanks”). Such collections of HBM allow twofold research. It allows to study the genetic variations in twins in the same environment (e.g. dizygotic twins) or, alternatively, the environmental effects of twins with an identical genetic background (e.g. monozygotic twins) (9). Examples of such twin banks are the Swedish, the Danish and the Netherlands Twin Registry and the European project GenomEUtwin.

[12] http://www.ukbiobank.ac.uk/

1.4.2.2 Disease-oriented, clinical or hospital-integrated biobank

A disease-oriented biobank, also called a clinical or hospital-integrated biobank (3), contains HBM in relation to specific pathological conditions. The HBM is collected from individuals in the framework of medical diagnosis or treatment. An important example of such disease-oriented biobanks are tumour biobanks(44). In this case HBM and data are usually collected from patients. This type of biobank is therefore typically integrated into a hospital (4). The types of HBM stored in this type of biobank are tissues, isolated cells, blood, urine or saliva. The HBM (and data) in this type of biobank can be used to study the different stages and the treatment of a particular disease at the molecular level. One can identify biomarkers that can be used for the prediction, diagnosis, and response to the treatment of a particular disease. In addition, the identification of novel pathways involved in a particular disease can lead to the discovery of new molecular targets. These molecular targets may, in turn, result in the development of more specific medicines. This type of biobank is used for at least two types of studies (9,25,31).

Case control studies are a first type of studies that use HBM and data from disease-oriented biobanks. In this case HBM and data are stored both from both healthy and diseased individuals. The comparison of HBM and data from both groups can provide insight in certain disease profiles and mutant genes. It can furthermore be used to study the interaction between genetic and environmental factors(31). The HBM of the control group may be obtained from the collection of a population-based biobank (9,25,31).

Prospective studies are another type of studies that use HBM and data from disease-oriented biobanks. HBM and associated data is collected to study the interaction between genetic factors and the response to treatments(31). Most biobanks contain in addition to the affected tissue also unaffected tissue from the same patient. This allows a direct comparison of changes at the genetic level (9,25,31).

An example of a disease-specific biobank is the Spanish HIV HGM Biobank. This biobank was created in 2004 to collect and provide access to distinct HBM from HIV/AIDS Patients. The HIV HGM Biobank receives HBM (and data) from 37 hospitals in Spain and organizes those HBM in 7 cohorts of HIV-patients according to specific criteria: (i) Cohort of Adults; (ii) Cohort of Long-Term-Non-Progressors; (iii) Cohort of Rapid Progressors; (iv) Cohort of Acute Infection; (v) Cohort of Lymphocyte-Non-regenerators; (vi) Cohort of HIV-infected patients with liver organ transplant and (vii) cohort of paediatric HIV-infection. The different cohorts of HBM and data are accessible – free of charge – for national and international research projects[13].

[13] http://www.esbb.org/biobanks-featured.html

1.5 Biobank networks

1.5.1 Concept of biobank networks

Access to large amounts of HBM and data is crucial for many biomedical research projects. That is why several initiatives have been taken to develop biobank networks to share and combine different collections of HBM and data. The concept of a 'biobank network' can be defined as '*a group of institutions who freely assume the commitment to collaborate in the domain of biobanking and who (often) share the same procedures and quality policies, and who are (or might be) helped by a central hub for coordination in terms of service'* (1).

1.5.2 Classification of biobank networks

Biobank networks are developed for various purposes. These could be the development of standard operation procedures (SOPs) in relation to the governance of biobanks and the quality of HBM and associated data, the collection and sharing of HBM and data or the creation of common research infrastructures(26,45).

Shickle, Griffin and El-Arifi distinguish seven different types of biobank networks. Quite a lot of the existing networks are a mixture of these seven different types(45).

The primary purpose of a *storage network* is to provide common storage facilities. This enables the participating biobanks to reduce their costs. The savings generated by such a network could be invested in technology to increase the quality of the HBM. Every participating biobank is given a certain storage capacity within the common facilities. The individual biobanks remain the custodians of their HBM and data. They maintain the right to control how to provide access to their collection. An example of such a network is the "Singapore Tissue Network"(45).

Bring-and-share storage networks could be considered a subtype of the storage networks. Participating biobanks that make their HBM and data available to other participants pay a lower fee compared to those participants that only use storage facilities. Participants can request that their HBM and data will only be available to other researchers after completion of their own research project. In this case they may have to pay an additional fee for such "preferential access." An example of such a network is the Istituto Nazionale per la Ricerca sul Cancro, Biological Bank and Cell Factory in Italy(45).

A third type of biobank network is the *catalogue network*. This type of network consists of a central database where researchers can search whether the participating biobanks provide access to particular HBM and data for use in their research project. The HBM and the data are stored at the facilities of the participating biobanks. The biobank network only provides access to a minimum dataset to search the different collections. This type of network is particularly useful when a researcher wants to have access to rare HBM and an individual biobank cannot provide sufficient amounts of such HBM. Examples of such type of network are the Belgian Virtual Tumourbank (BVT) and the OECI-TuBaFrost consortium (45).

Partnership networks are based on a formal partnership agreement between the different participating biobanks. This agreement may contain rules on how to collaborate. It could develop common rules on the storage and processing of HBM and data as well as rules and procedures that apply when researchers want to access the collection of HBM and data. The partnership aims to share knowledge between the different partners. The collections of HBM and data of the different partners can either be stored at one central location or can remain at the facilities of the different partners. Usually the partnership will create a central hub to manage the coordination and the administration of the network. A common catalogue allows researchers to search the collection of HBM and data. The partnership network could hold custodianship and therefore decide on access to HBM and data collected in the framework of the network. The partners could maintain the right to decide on access to HBM and data that was collected prior or outside the network. The partners need to agree on what will happen with the collection of HBM and data in case the network would dissolve. An example of a partnership network is the “Victorian Cancer Biobank” in Australia(45).

A *contribution network* could be described as a collaboration between a biobank and clinicians or researchers. Clinicians and researchers provide the biobank with valuable or rare HBM and data that they collected in the framework of their clinical or research facilities. The biobank will usually store and govern the collection of HBM and data at a central facility. Custodianship over the collection HBM and data will be exercised by the biobank. It will also be the biobank that decides on access to the collection for research purposes. Professional organizations or associations of clinicians and researchers that are active in a particular disease domain may set up such contribution networks. An example of such a contribution network is the "Paediatric Tumour bank" in Australia (45). One could argue that another example would be the initiatives taken by some hospitals to store and manage HBM and data collected in their different departments, in a central facility. We see examples of this in Belgium and other countries

A sixth type of network is called *expertise networks*. This type of network focuses on the sharing of expertise and does not involve the exchange of HBM and data. Quite a lot of those initiatives are active in matters concerning ethical, legal and societal issues (also called ELSI issue) in relation to biobanks. Some of those initiatives aim to encourage the harmonization of SOPs or access rules and procedures. Examples of such networks are the ‘Public Population Project in Genomics and Society’ (P^3G), the International Society for Biological and Environmental Repositories (ISBER), the European, Middle Eastern & African Society for Biopreservation and Biobanking and the National Swedish Biobanking Programme (45).

Networks of population cohorts are the final type of networks mentioned by Shickle, Griffin and El-Arifi(45). The participating biobanks of such network are prospective or retrospective population cohorts. Such cohorts comprise of HBM of adults or children in a particular population or a part of such population. The creation of networks between population cohorts can enlarge the possibilities to study common causes of morbidity or mortality. The collaboration between population cohorts is particularly important in relation to rare disease. In this case the different participating cohorts might only dispose of a limited number of HBM affected by such rare disease. Only a limited number of networks of

population cohorts exist(45). One could consider the 'European Prospective Investigation into Cancer and Nutrition (EPIC) study' as a network of population cohorts[14]. EPIC is a "*multi-centre prospective cohort study designed to investigate the relation between diet, nutritional and metabolic characteristics, various lifestyle factors and the risk of cancer and other chronic diseases*"(46). EPIC recruited more than 500.000 donors across 10 European countries and is one of the largest cohort studies in the world. EPIC consists of several national or regional cohorts, such as EPIC-Denmark and EPIC-Germany.

1.5.3 Examples of biobank networks in Europe, the Benelux and Scandinavia

We hereunder to provide examples in the Benelux, Scandinavia and Europe of some of the different types of biobank networks mentioned above. Some or all of the networks described hereunder, could be considered a mixture of different types.

The 'Karolinska Institutet Biobank' in Stockholm (Sweden) could be considered a combination of a storage network and a network of cohorts. The Karolinska Institutet Biobank manages many different types of collections of HBM and data. Some collections are stored and managed at the request of researchers or health care authorities. The Karolinska Institutet Biobank however also manages HBM and data collected in the framework of large population-based cohorts – such as TwinGene cohort[15], the '60-year old cohort'[16] and the LifeGene[17] cohort – and in the framework of disease based studies. The Karolinska Institute biobank offers different types of services to the principal investigators that store their HBM and data in the biobank Such services cover (i) advice on the planning and the ethical and legal compliance of a study; (ii) the registration, processing, storage and withdrawal of samples; and (iii) DNA extraction(47).

The Belgian Virtual Tumourbank[18] (the 'BVT') is an example of a disease-specific, catalogue network. The Belgian Virtual Tumourbank was official created in 2008 as a result of the Initiative 27 of the Belgian National Cancer Plan. The general aim of this initiative was the promotion of translational cancer research and the collaboration between cancer researchers in Belgium. The BVT consists of 11 hospitals, among which the major Belgian university hospitals. A Royal Decree of 20 September 2009 indicates the conditions that a hospital has to meet to receive financing for its participation in the BVT. The tumour samples and associated data are stored and managed by the biobanks participating in the BVT. The Belgian Cancer Registry coordinates the activities of the BVT. It created – in collaboration with the different biobanks – a central database with minimum datasets on the available residual human tumour samples. A coded version of the central database is accessible to research groups, which allows them to search for HBM and data that could be interesting for their research projects. When a researcher wants to use particular HBM and data in his research project, he has to submit an access request to the local biobanks that store and manage the HBM and data (48).

[14] http://epic.iarc.fr/about/cohortdescription.php
[15] http://ki.se/en/meb/twingene-and-genomeeutwin
[16] http://ki.se/en/imm/the-60-year-old-cohort
[17] http://lifegene.ki.se/
[18] http://www.kankerregister.org/tumourbank.aspx?url=BVT_home

Another biobank network initiative in Belgium is the creation of a Flemish Biobank by the Centre for Medical Innovation (CMI). The CMI was officially founded in December 2009 at the initiative of the Flemish Government, the Flemish Ministry of Economy and Scientific Affairs, the 5 Flemish University Medical Centres and representatives from the Health Care Industry. The first project of CMI was the creation and coordination of a Flemish biobank. This will be a virtual biobank (network), which focuses on specific diseases fields. CMI developed harmonized quality criteria for HBM and accompanying clinical data sets. It emitted a report, entitled the 'Ethical and Legal Framework applicable to Biobanks." CMI furthermore aims to create a central IT backbone that should result in a database that would allow translational research projects between different universities and/or industry[19]. The different participating hospitals maintain the custodianship of their collections of HBM and data. In the future the Flemish Biobank initiative aims to establish collections of HBM and data *"in disease domains in which the Flemish knowledge institutes and Flemish industry has a strong position*." Pilot biobanks will be set-up in the 5 disease domains: (i) sudden cardiac death; (ii) diabetes; (iii) inflammatory bowel disease; (iv) rheumatic arthritis and (v) diabetes(49).

Another initiative that could – to a certain extent – be considered a catalogue network is the Danish National Biobank initiative. The initiative created an online registry that enables researchers to access the combined data of all Danish biobanks that participate in the initiative. In the future the Danish National Biobank Registry wants to provide an overview and access to more than 15 million HBM – relating to different diseases – in existing and future collections. When a researcher has found the HBM and data that he wants to use in a research project, he should contact the Coordinating Centre that will assist him in obtaining access to the HBM and data[20].

The OECI-TuBaFrost consortium is a European virtual biobank network (or catalogue network) that brings together biobanks specialized in cancer. The consortium initial started as a research project funded by the 5th Framework Programme of the European Union. Later the project resulted in the creation of a consortium between the different participating biobanks. From 2006 until 2010 the TuBaFrost Consortium was integrated into the Organisation of European Cancer Institutes (OECI) Pathobiology working group. This working group supports the European virtual biobank infrastructure in the management of the exchange platform OECI-TubaFrost. The further development of OECI-Tuba Frost has been possible through support from the EurocanPlatform project. The OECI-TuBaFrost exchange platform contains a central database application. This application allows to search which HBM and data are available in the collections of the different participating biobanks. The platform supports the exchange of HBM and data within a project consortium. Access to such HBM and data is limited to the members of the consortium, while the database is accessible to all OECI members(50,51).

[19] http://cmi-vzw.be/history.htm
[20] http://www.biobankdenmark.dk/About%20the%20Biobank.aspx

The Parelsnoer Institute in the Netherlands could be considered a diseased-focused, partnership network. This initiative is a collaboration between all eight Dutch university hospitals. Its aim is to create a national research infrastructure for clinical epidemiology(31). The Parelsnoer Institute consisted in 2007 of eight cohorts. They each focus on one syndrome, also called pearls. These different syndromes are: inflammatory bowel disease, rheumatoid arthritis, stroke, hereditary colon cancer, leukaemia, neurodegenerative diseases, kidney failure and diabetes. Those eight syndromes were chosen due to their importance for the Dutch health care system. In the course of the project new cohorts have been added in relation to the following syndromes: CONCOR (congenital heart defects), endocrine tumours, ischemic heart disease and pancreas(52). One expects to accelerate research by focusing on the collection of HBM and data and research projects concerning a limited number of syndromes(53). The cohorts provide access both to HBM and data collected in a prospective manner(54).

An example of an international expertise network is the Public Population Project in Genomics and Society (P³G). P³G is a not-for-profit consortium. It provides the international research community with online access to expertise, tools and services in relation to ethical, legal, social, epidemiological and technical issues with respect to (population-based) biobanks. P³G also manages an online catalogue with information on large-population based biobanks. Finally P³G participates in the development of the BRIF (Bioresource Research Impact Factor)[21].

The 'Biobanking and Biomolecular resources Research Infrastructure' (BBMRI) was initiated in 2008 under the European Research Infrastructure Preparatory Phase of the ESFRI roadmap. It was funded by the European Union (9,10). The preparatory phase of BBMRI lasted for three years and came to its end in January 2011. On 3 December 2013, BBMRI was officially awarded the Community legal framework for a European Research Infrastructure (ERIC). BBMRI-ERIC[22] is established as a pan-European (distributed) research infrastructure and network. It consists of existing and *de novo* population-based and disease-oriented biobanks, as well as biomolecular resources. The aim of BBMRI-ERIC is to facilitate access to the different biobanks and biomolecular resources and to support high quality biomolecular and medical research (37). That is why BBMRI-ERIC wants to act as an "umbrella network" that contributes to the development of common standards and a clear ethical and legal framework(9,10). A general inventory of the different participating biobanks and biomolecular resources is currently being created as well as common access requirements (9,10). The structure of the BBMRI network is represented as a "disturbed hub and spoke scheme" (see Figure 1). In this scheme, the various biobanks, biomolecular resources and specialized technology centres are connected via their specific hub.

[21] http://p3g.org/about-p3g/glance
[22] The Biobanking and Biomolecular resources Research Infrastructure-European Research infrastructure consortium

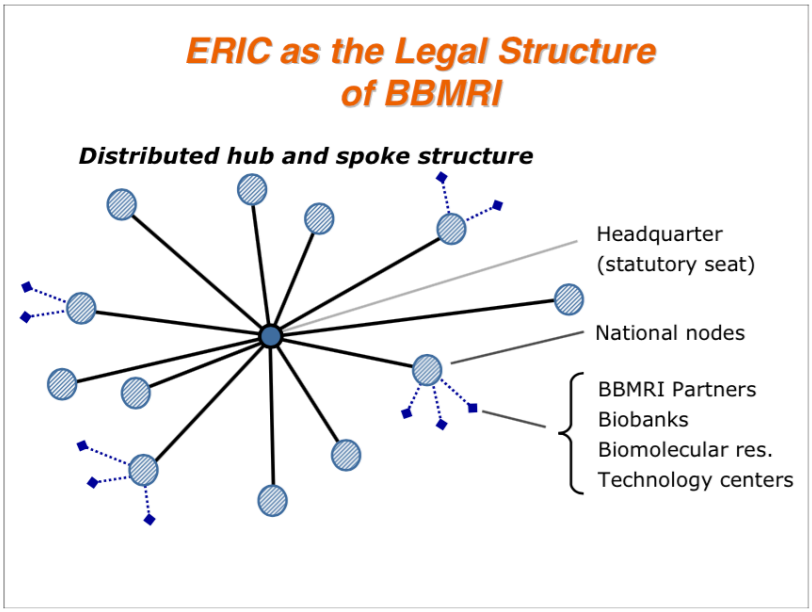

Figure 1: Distributed hub and spoke structure of BBMRI

Each participating country has its own national hub or node. This hub coordinates the national biobanks, biomolecular resources and technology centres and links its activities with the pan-European activities of BBMRI-ERIC. National hubs have been created or are being created in Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany Greece, Italy, Malta, the Netherlands and Sweden. Norway, Poland, Switzerland, Turkey and IARC[23]/WHO are observers to BBMRI-ERIC. Sweden, Norway, Denmark, Finland, Iceland, the Faroe Islands and Estonia have created BBMRI Nordic. BBMRI Nordic is a network comprising national infrastructures of those Nordic countries engaged in facilitating biobanks activities. The BBMRI-ERIC consortium today consists of more than 59 members and 225 partners from more than 30 European countries. The headquarters of BBMR-ERIC are established in Graz in Austria. The headquarters coordinates the interaction between different national hubs. It created a virtual search platform that provides access to research resources, facilities and expertise, available in the different participating countries[24].

[23] The International Agency for Research on Cancer http://www.iarc.fr/
[24] http://bbmri-eric.eu/2

1.6 Legal framework applicable to 'access to biobanks'

Different legal instruments determine the legal framework applicable to access to biobanks.

The PhD project will study both binding legal instruments – such as international treaties or national legislation – and non-binding normative instruments or soft law that apply to access to biobanks. The PhD project will also study access arrangements and 'key access conditions'.

The most important binding legal instruments (or sources of law) at the international level are international conventions or treaties concluded between two or more countries. Other sources of law are international customs, general principles of law and judicial decisions of international courts(55).

Binding legal instruments at the level of the European level are the Treaty on the European Union and the Treaty on the Functioning of the European Union. These Treaties contain the basic provisions on the European Union's objectives and organizations. The main secondary sources of law at the level of the European Union are regulations and directives.

The most important binding legal instruments at the national level are laws enacted by the national parliament. Other binding legal instruments at the national level are executive decrees – such as Royal and Ministerial Decrees – that implement national laws.

Additional sources of law are non-binding normative instruments or soft law. The Oxford Dictionary of Law defines soft law as "*guidelines of behaviour, such as those provided by treaties not yet in force, resolutions of the United Nations, or international conferences, that are not binding in themselves, but are more than mere statements of political aspiration*." Two important examples of such soft law are the Recommendation (2006)4 of the Council of Europe or the Helsinki Declaration.

Another non-binding sources of law are access arrangements. Access arrangements can be defined as "guidelines, best practices, opinions, policies, agreements, etc. containing rules on access to and use of HBM and data collections stored within biobanks'.

2 Scope

The project covers the various aspects of the legal framework applicable to 'access to biobanks' (see Figure 2).

We define 'access to biobanks' for the purpose of this PhD project as 'the relationship between the custodian of a biobank and a researcher who applies for access to HBM and data stored in a biobank (i.e. an applicant)'.

We decided to focus on 'access to biobanks', since few research projects had studied this topic when this PhD project was initiated. We decided not to study the – without any doubt – important relationship between the custodian of a biobank and the donor/patient, since many previous research projects focused on the role, the participation and the expectations of the 'donor'(56–62). That is also why we did not focus on the topics of biobank governance, consent and return of incidental findings (23,63–70).

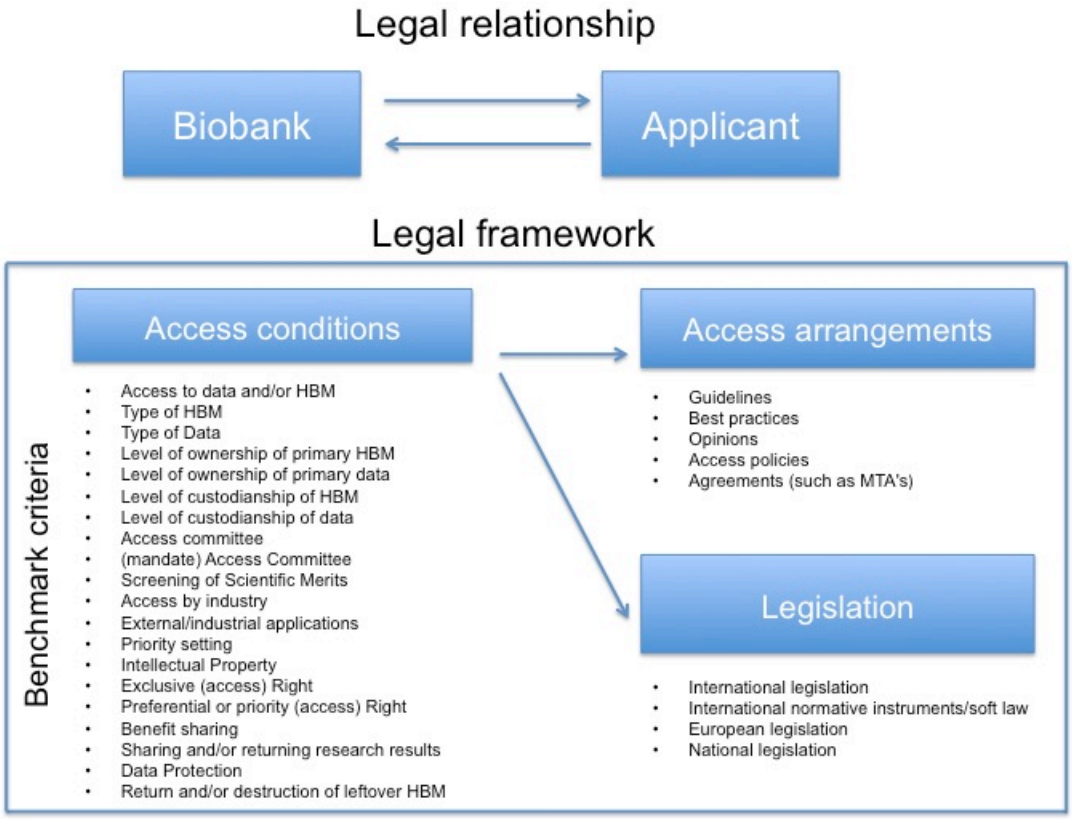

Figure 2 Graphical representation of scope of PhD

2.1 Objectives and research questions

In an interdisciplinary context, the general objective of the project is to contribute to the creation of a clear and smooth legal framework – i.e. legislation, non-binding normative instruments and access arrangements – applicable to access to and use of HBM and data stored in biobanks.

The specific objectives of the project are:

- to assess to which extent access arrangements contain information on 21 identified 'key access conditions' (Chapter 1)
- to assess the variation in how access arrangements apply those key access conditions to elucidate potential for harmonization (Chapter 2);
- to investigate how access arrangements are applied in practice (Chapter 2);
- to study the rights and obligations of custodians and applicants and - to a limited extent donors – as stipulated in the legal framework applicable to access to biobanks (Chapter 3);
- to study the relationship between IPRs and biobanking and the sharing of research results (Chapter 4)

Finally, Part 4 of the PhD formulates concluding findings and recommendations on a transparent, feasible and encouraging legal framework applicable to biobanks.

The research questions of the project are:

- Which legal framework determines the relationship between a biobank and a researcher applying for access to HBM and data stored in a biobank? (Chapters 1, 3 and 4)
- Does the existing legal framework correspond to the needs of biobanks and other stakeholders? (Chapters 2 and 4)
- To which extent is additional legislation or soft law required for the creation of a feasible and encouraging legal framework for biobanks? (Discussion and recommendation)

The research questions apply in a transversal and horizontal way to the different chapters of the PhD project. The different research questions are studied in several chapters across the thesis and answered in the discussion and recommendation chapter.

2.2 Methods

Theoretical (legal) and empirical (qualitative) research methods were designed and used to perform the studies, including literature (scientific and legal) reviews, interviews and in-depth document analyses. The specific methodology used in each study is described in the different chapters. We nevertheless wanted to explain the general methodological choices made in the development and the conduct of the PhD project.

The legal framework applicable to 'access to biobanks' is still a relatively new field. It is therefore no surprise that there is no overall consensus or general theory to delineate the legal framework that applies to 'access to biobanks'. There are furthermore no 'general accepted' key conditions or

benchmark criteria to be taken into account when evaluating the legal framework applicable to 'access to biobanks'. Due to the novelty of this field, we were not able to apply a specific, existing theoretical perspective as benchmark for our study[25]. We attempted to apply the 'social constructivist theory'[26] of ownership to develop the empirical study described in Chapter 2. According to this theory, "*ownership is the result of a series of social choices and events that could well have been different*." This theory does not aim to answer the absolute question whether a particular stakeholder – such as the custodian, the applicant or donor – can be the 'owner' of HBM. Instead, the theory considers it more useful to see ownership as bundles of rights and obligations of different stakeholders in relation to a particular object. Such rights could include for instance the right to decide on the use of HBM, the right to transfer HBM, but also the obligation to protect the interests of the donors. Chapter 2 studied the different perspectives of stakeholders in relation to these (bundles of) rights and obligations. Since the theory of 'social constructivism' focuses on 'ownership', it did not allow us to provide a complete answer to the research question 'which rights and obligations are held by stakeholders in relation to HBM and data?' It appeared not possible to define the complete bundle of rights and obligations of the stakeholders.

Although we did not apply a particular theoretical perspective, we did make a number of methodological choices in how to study the legal framework to access to biobanks.

First, we decided to study the legal framework from a continental (or civil) law perspective, rather than a 'common law perspective'. This is due to the fact that the majority of the countries within the European Union apply a 'continental law perspective' and the PhD candidate was trained in a country with a continental law tradition, in particular Belgium. The main source of law in a 'continental law' approach is legislation enacted by the legislator (the national parliament); the judicial courts are only expected to apply the law. In a common law system the decisions of judicial courts are considered much more as an important source of law. The 'common law' system is applied amongst others in the United Kingdom, the US and Australia(71). The fact that we applied a 'continental law' approach implies that the recommendations of the PhD project might be mainly useful to study the legal framework applicable to access to biobanks in 'continental law' countries and less in 'common law' countries.

Second we decided to apply a 'legal positivistic' approach rather then a 'legal realistic' approach. This implies that we attempt to describe and explain the legal framework applicable to access to biobanks, but we do not evaluate the moral value of such legal framework. We will therefore not prescribe how the legal framework 'ought to be'(55). We choose the 'legal positivist' approach, since this approach is

[25] We would like to remark in this respect that it is not uncommon that a legal research project does not start from a particular theoretical perspective. A. Dyèvre remarks in this respect that "*EU law scholars tend to comment on legal developments without feeling the need to ground their analysis in explicit theoretical assumptions*(72)." The main aim of legal studies is often to (a) provide a thorough description of the applicable legislative framework, (b) study how the framework should be applied in a specific context, (c) try to explain the application of the legal framework. That is why legal research projects are often more descriptive in nature.

[26] Quigley, M. Property and the body: applying Honoré. *J MED ETHICS* **33,** 631–4 (2007).
28; Björkman, B. Different types--different rights. Distinguishing between different perspectives on ownership of biological material. *Science and engineering ethics* **13,** 221–33 (2007)

most often applied in the study of continental law systems. The 'legal realist' approach is mainly applied to study the US 'common law' system. The 'legal realist' approach is not very often used by European legal scholars(72).

Third, we decided to study the legal framework in the material – or broad – sense and not in a formal – or narrow – sense. This implies that we deliberately decided not to limit our analysis to the binding legal instruments – such as international treaties or national legislation – that apply to access to biobanks, but also to study non-binding normative instruments or soft law – such as recommendations or guidelines that determine the legal relationship between the custodian of a biobank and an applicant. We felt that the study would be incomplete, if we would restrict ourselves to an analysis of the law in the formal sense, i.e. the legal instruments or norms that are adopted by legislator in this area and that are binding on legal subjects. Afterall the formal legal norms that exists in relation to access to biobanks are limited. Furthermore one can argue that non-binding normative instruments have an equally important impact on the legal framework that applies to "access to biobanks". One can refer in this respect to the Recommendation (2006)4[27] of the Council Of Europe. Although the Recommendation is a non-binding normative instrument, it nevertheless had an important impact on access arrangements developed by biobanks and legislation enacted by national legislator in relation to the use of HBM and data in biomedical research.

Fourth we decided to study the legal framework applicable in one Benelux country and one Scandinavian country, since we are based in the Benelux and the Scandinavia countries are considered as pioneers in biobanking(18,73,74). We decided to compare Belgium and Denmark for a number of reasons. First, the comparison between both countries appeared interesting, since Denmark has a very strong reputation in biobanking, but explicitly decided not to develop specifically legislation on biobanks and the use of HBM and data in biomedical research. Belgium at the other hand did develop specific legislation on biobanks. Denmark is also an interesting country from a legal point of view, since the Danish Data Protection Agency has specific competence in relation to biobanks. This is not the case in Belgium and most other countries. Finally we choose to compare Belgium and Denmark for practical reasons. The PhD candidate has worked in both countries and therefore had the opportunity to gain deeper knowledge on the legal framework applicable to biobanks in Denmark and Belgium. Due to time constrains we were not able to study more countries.

Fifth, we decided to define and use 'key access conditions' as benchmark criteria to study and evaluate the legal framework that applies to access to biobanks. This was inspired by the idea that an optimal legal framework "should be based upon a coherent set of principles (or conditions), to ensure that the law is consistent, effective and relevant for researchers and society"(75). Since no general consensus exists on such 'key access conditions', Chapter 1 started with a review of international literature and reports of P^3G (4,76) and the Medical Research Council and The Wellcome Trust (69) on 'access to biobanks'. This allowed us to determine a set of conditions that are key to 'access to

[27] Recommendation Rec (2006)4 of the Committee of Ministers to Member States on Research on Biomedical Materials of Human Origin

biobanks' (see Chapter 1, Table 1). The key access conditions allowed us to determine which legal instruments to take into account when studying the legal framework applicable to access to biobanks. We decided in particular to study the combination of key access conditions (Chapter 1), access arrangements (Chapter 1), access practices (Chapter 2) and legislation (Chapter 3) to determine the legal framework applicable to 'access to biobanks' (see Figure 2). The 'key access conditions' were furthermore used (a) to describe the legal framework applicable to 'access to biobanks'; (b) to evaluate how the different legal instruments address 'access to biobanks' and (c) to which extent those instruments contribute to the creation of a transparent, feasible and encouraging legal framework.

We are aware that the set of conditions – used in the project – is not generally accepted. Some might argue that some 'access conditions' are missing – such as consent and cross border transfer of HBM and data – or that some conditions might not be considered as key to access to biobanks – such as intellectual property rights or the protection of personal data. We decided not to include the important principle of 'consent' in the set of access conditions, since we believe that consent mainly pertains to the relationship between the donor/patient and the biobank; it only indirectly relates to the relationship between the biobank and the applicant. Many previous research projects furthermore focused on 'consent'. Chapter 3 nevertheless looked into the legal framework applicable to 'consent' to the extent that this was relevant for 'access to biobanks'. We decided not to include the 'cross border transfer of HBM' as key access conditions, since we believe that it does not directly relate to ''legal relationship between the custodian of a biobank and an applicant'. The topic rather relates to the question whether a particular country allows the import or export of HBM and data. We did include the 'protection of personal data', since a biobank needs to comply with the legal rules in this respect in the development of access arrangements. We also included 'intellectual property' as a key access condition, since we believe that it might be considered as an important condition to protect the substantial investments made in biobanks and the results of research projects using HBM and data stored in biobanks.

2.3 Overview of PhD project

Chapter 1 of the PhD reports on a comparative document analysis of access arrangements of organizations, biobank networks and biobanks. This analysis provides qualitative data on the extent to which access arrangements contain information on 21 selected access conditions. It furthermore studied to which extent access arrangements implement those access conditions in a harmonized way.

Chapter 2 of the PhD reports on an empirical study of access practices in the context of biobanking. Interviews were conducted with stakeholders and experts to gain a more profound understanding on how access arrangements are applied in the daily practices of biobanks and biobank networks. This study aimed to gather practical experiences and personal opinions of the interviewees rather than factual information. The interviews provide qualitative data on the different perspectives held by stakeholders in relation to the rights and obligations of custodians, applicants and donors with respect to access to HBM and data stored in biobanks. This chapter allowed us to explain the lack of clear information on several 'key access conditions' and the high variation in the application of key access conditions. It also allowed us to investigate on which 'access conditions' consensus could be reached between stakeholders and which 'access conditions' remained unresolved. This might offer a deeper understanding on whether harmonization is possible on some key 'access conditions'.

Chapter 3 of the PhD reports on a comparative study of the legal framework that is applicable to access to biobanks. The comparative study started with a general overview of the national legislation applicable to biobanks in Belgium, Denmark and normative norms at the international level and at the level of the Council of Europe. It furthermore analysed the rights and obligations of custodians of biobanks, applicants and - to a lesser extent– donors in these different legal instruments. We investigated to which extent and how key 'access conditions' are regulated via the different legal instruments– in a broad sense – applicable to access to biobanks. That is also why we only describe and explain the different legal instruments to the extent that they are relevant for 'access to biobanks'.

Chapter 2 and 3 allowed us to determine which key 'access conditions' are sufficiently regulated via access arrangements or legislation and which are not sufficiently regulated.

Chapter 4 of the PhD reports on a legal study on intellectual property rights (IPRs) in biobanking and to a lesser extent the 'return and sharing of research results'. We studied those two key 'access conditions', since 'access arrangements' and legislation contain little information on those conditions, while they are nevertheless important for 'access to biobanks'. This legal study provides an overview of the most relevant IPRs in biobanking and discusses the risks and opportunities associated with the identified IPRs for an effective protection and use of biobanks in translational research and innovation. It furthermore touches upon the question whether biobanks should require the return and sharing of research results.

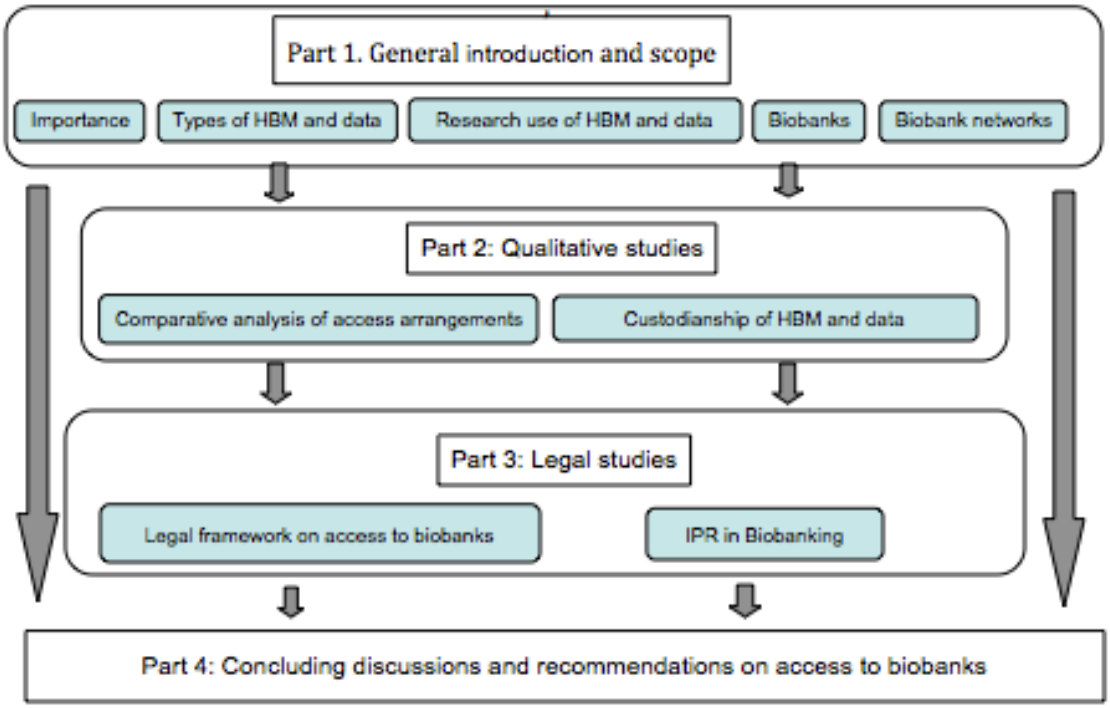

Figure 3: Overview of the PhD project

Part 2: Qualitative studies

Chapter 1: Access to biobanks: Harmonization across biobank initiatives

This chapter is based on:

Verlinden M, Nys H, Ectors N, Huys H

Access to Biobanks: Harmonization across biobanks initiatives.

Biopreserv Biobank. 2014; 12(6):415–22.

1 Introduction

Access to human biological materials (HBMs) and associated data stored in biobanks is crucial for biomedical research (14,16,17). Researchers need to be able to efficiently access different collections of HBMs and data (69,77,78). In order to guarantee their long-time sustainability as well as the scientific, legal and ethical correct use of HBMs and data, biobanks and biobank networks need to exercise control on the access to their resources (1,14,16,69,70,77). Taken into account the above, it is not surprising that several organizations and authors have stressed the importance of clear and transparent rules on access (4,16,63,69,77,79–85).

Previous empirical studies focused on guidelines and policies in relation to (amongst others) governance, consent and return of incidental findings (23,63–68). Only a few empirical studies have focused on access arrangements (16,63,69,77,81,82), i.e. 'guidelines, best practices, opinions, policies, agreements, etc. containing rules on access to and use of HBM and data collections stored within biobanks' (a similar definition of access arrangements is used by S. Fortin *et al.* (16) and the OECD(86)).Previous empirical studies on access arrangements tended to focus on a limited number of access conditions or studied a limited number of access arrangements (4,63,69,76,77,81,82).

The current study provides qualitative data on the extent to which access arrangements contain information on 21 selected key access conditions and the level of harmonization of these conditions.

2 Methods

2.1 Document selection and collection

Twenty-seven international, regional and national organizations in the European Union, the United States, Canada and Australia were identified (see Annex 1). In addition, a literature review on access to HBMs or data, supplemented with information from the Public Population Project in Genomics and Society (P^3G), the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI.ERIC), the Deutscher Ethikrat and the Institute for Prospective Technological Studies (IPTS) of the European Commission's Joint Research Centre (JRC), served as a basis to develop an overview of 51 biobank networks and 22 biobanks worldwide (see Annex 1)(4,76,87–89). The majority of the identified biobank initiatives[28] were established and funded by not-for-profit institutions. Limited information was found for biobanks funded by for-profit institutions. The comparative study focused on access to HBMs or data or both for purposes of biomedical research.

[28] The term 'Biobank Initiatives' covers biobanks, biobank networks as well as organizations

2.2 Access to publicly available access arrangements

Websites and (scientific) publications available in English, French, Dutch, German or Spanish were reviewed in order to retrieve publicly available access arrangements of the selected biobank initiatives. In case no access arrangement was found, the contact person of the biobank initiative was contacted via e-mail with the question whether it developed an access arrangement and could provide a copy of such arrangement. In the absence of a response, one reminder was sent.

2.3 Identification of 21 key access conditions for biobanking

In a preparatory phase, international literature in relation to access to HBMs or data was reviewed using online resources (PubMed, Embase and Web of Science). The terms 'biological specimen bank', 'biobanking', 'biobank', 'biological repository' and 'research' were used to review these resources. The literature (4,9,16,25,63,66,80,90) was supplemented with information found on the website of P^3G (4,76) and a report drafted at the request of the Medical Research Council and The Wellcome Trust (69). This allowed us to identify 21 key conditions in relation to access to HBMs and data (see Table 1). It was decided not to focus on consent, since this has been investigated extensively in previous studies (23,63–66,69,70).

Table 1 Overview of key access conditions

Key access conditions	Description
1. Access to data and/or HBM	Does the access arrangement apply to data, HBM or both?
2. Type of HBM	To which type of HBM does the access arrangement apply?
3. Type of data	To which type of data does the access arrangement apply?
4 & 5. Level of ownership of primary HBM and data	Which level (biobank network, biobank or PI) holds ownership over primary HBM and primary data?
6 & 7. Level of custodianship of HBM and data	Which level (biobank network, biobank, funder or PI) holds custodianship over HBM and data?
8. Access committees	To which extent does the access arrangement provide for a committee to decide on access to HBM, data or both?
9. Mandate access committee	How is the mandate of the access committee specified in the access arrangement?
10. Screening of scientific merit	Does the access arrangement provide for a screening of the scientific merit of access requests and how?
11. Access by industrial company	What does the access arrangement provide in relation to access by industrial companies to the HBM and/or data?
12 & 13. External/industrial applications: Different legal conditions and fees	To which extent does the access arrangement provide different legal conditions and fees for external or industrial applications compared to internal applications?
14. Priority setting	Does the access arrangement provide criteria to prioritize parallel applications and if this would be the case, which criteria are stipulated?
15. Intellectual property	What does the access arrangement provide in relation to IP rights held by the biobank?
16. Exclusive (access) right of applicant	To which extent does the access arrangement provide the applicants exclusive access to certain HBM and data?
17. Preferential (access) right of collector	To which extent does the access arrangement provide preferential (access) to collectors who provided HBM and data to the biobank initiative?
18. Benefit sharing	To which extent does the access arrangement stipulate an obligation to share benefits resulting from the use of HBM and/or data?
19. Sharing or returning research data or results	To which extent does the access arrangement stipulate an obligation to return to the biobank initiative or share with third parties research data or results?
20. Data protection	To which extent does the access arrangement provide access to coded, anonymised or identifiable data?
21. Return and/or destruction of tissue	To which extent does the access arrangement stipulate an obligation to return and/or destroy leftover tissue?

Note: We wish to clarify that the key access conditions are not listed in a hierarchical order in terms of importance.

2.4 Comparative analysis of access arrangements

In the second phase (August 2011 and January 2013, at which time two extra copies of access arrangements were obtained) a comparative analysis was conducted of the access arrangements. Although access arrangements of organizations, biobank networks and biobanks might not be entirely comparable – taken into account their different characteristics and purposes –, access arrangements of each category of biobank initiatives, nevertheless, have an influence on the question whether access conditions are harmonized. We therefore studied the access arrangements of all three categories of biobank initiatives, investigating the trends and differences within as well as between each category, and addressing the question whether access arrangements promulgated by organizations influence those of biobank networks and biobanks. First it was investigated to which extent each of those arrangements contained information in relation to the 21 key access conditions identified in the literature review (4,16,63,69,76,81,82). If available, the information on the key conditions was summarized and compared using predefined templates[29]. When access arrangements did not explicitly refer to one or more of the 21 access conditions under study, the text of the arrangement was interpreted to discover implicit information on such conditions. It cannot be excluded that some of these interpretations might not fully correspond with the real (unexpressed) intentions of the concerned biobank initiative. The comparative templates[30] allowed us to develop qualitative data illustrating the lack of clear information and harmonization in relation to the 21 selected access conditions (see Annex 2). Finally we investigated to which extent access arrangements of biobank initiatives applied the 21 selected access conditions differently depending on whether these initiatives were (rather) population- or hospital-integrated.

3 Results

We retrieved access arrangements of 26 organizations, 36 biobank networks and 20 biobanks. We were not able to obtain access arrangements of 1 organization, 15 biobank networks and 2 biobanks. Of those that we were not able to obtain, thirteen access arrangements were not publicly available and 3 were under development (thus also unavailable) in 2011. One organization and 1 biobank did not (yet) develop an access arrangement. We observed relatively few differences in how access arrangements of population- and hospital-integrated biobank initiatives applied the 21 key access conditions. Therefore we decided not to focus on the distinction between both types. Hereafter we describe in detail the results concerning 6 selected conditions that, according to the authors, represent the most remarkable findings. An overview of all the results of the comparative analysis can be found in the Annex 2.

[29] The template consists of a table enlisting the 21 key access conditions
[30] The comparative template consists of an excel sheeting that enabled us to compare the different access arrangements

3.1 Ownership

None of the access arrangements provided that the principal investigators became owner of basic HBMs and/or data that they collected and provided to the biobank initiative.

The majority of the access arrangements that provided access to HBM (14 organizations, 22 biobank networks and 13 biobanks) did not stipulate whether the biobank network, the biobank or the principal investigator held ownership rights in relation to the basic HBMs (see Figure 4).

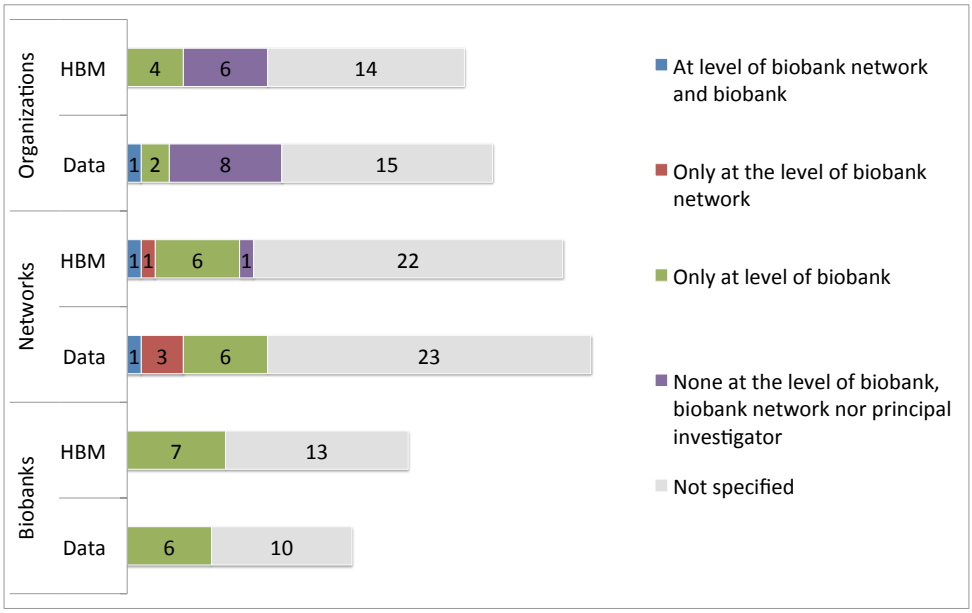

Figure 4: Ownership

The majority of the access arrangements that provided for access to data (15 organizations, 23 biobank networks and 10 biobanks) did not stipulate whether the biobank network, the biobank or the principal investigator held ownership rights in relation to the basic data (see Figure 4).

Access arrangements of 8 organizations (whereof 5 are organizations from the United Kingdom) explicitly provide that neither the biobank network, nor the biobank nor the principal investigator hold ownership in relation to basic data (as such).

The results revealed that the majority of access arrangements do not contain any information on whether any ownership is held in relation to HBM or data.

3.2 Level of custodianship

The level of custodianship over HBMs was not defined in the access arrangements of 11 organizations, 6 biobank networks and 4 biobanks.

With respect to biobank networks, 6 out of 31 access arrangements stipulated that the biobank network held (exclusive) custodianship over HBMs, while 15 stipulated that custodianship was held only at the level of the biobank (see Figure 5) and 4 stipulated that the biobank network and the biobank shared custodianship.

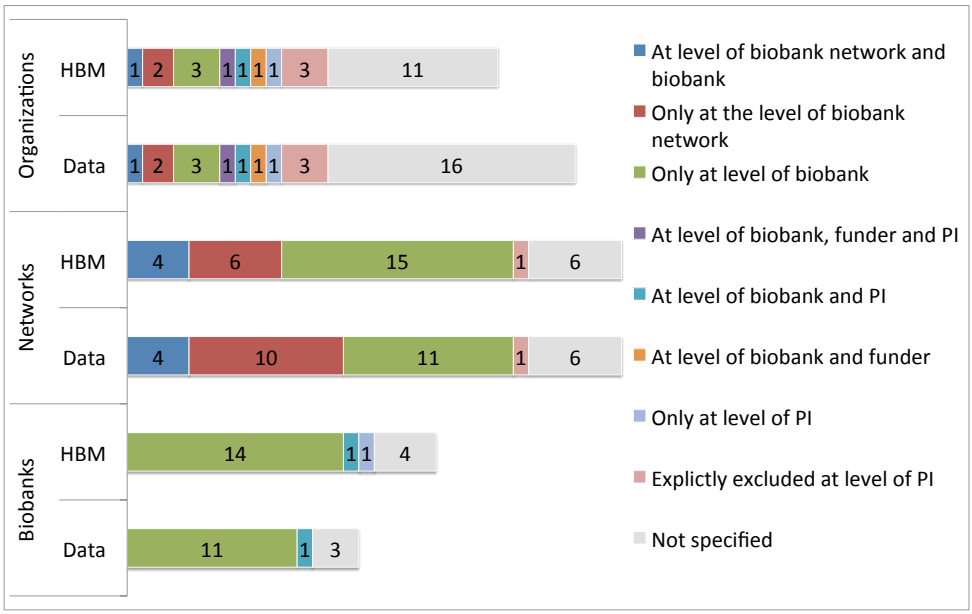

Figure 5: Custodianship

The access arrangement of 1 biobank provided for shared custodianship over HBMs between the biobank and the principal investigator, while the access arrangements of 14 biobanks granted custodianship to the biobank; the access arrangement of 1 biobank stipulated that the principal investigator held custodianship over the samples collected by him/her.

The level of custodianship over data was not defined in access arrangements of 16 organizations, 6 biobank networks and 3 biobanks.

With respect to biobank networks, 10 access arrangements stipulated that custodianship was held only at the level of the biobank network, while access arrangements of 11 biobanks networks stipulated that custodianship was held only at the level of the biobank. Access arrangements of 4 biobank networks provided that the biobank network and the biobank shared custodianship over the data.

3.3 Scope of custodianship

The comparative analysis revealed differences in how access arrangements defined custodianship. The following (common) elements were identified on the basis of the comparison: (i) the responsibility to safeguard the confidentiality, integrity and security of the collection and the interests of the donors. Custodianship could furthermore consist of (ii) the right to control the preservation, access, use, transfer and/or disposal of collections.

3.4 Access committees

The majority of the screened access arrangements (14 organizations, 23 biobank networks and 14 biobanks; see Annex 2) provided for the establishment of an access committee. One organization and 1 biobank network stipulated explicitly that no access committee should be established.

When we looked specifically at access arrangements establishing an access committee, we noticed that access committees of 11 organizations, 16 biobank networks and 12 biobanks provided advice or decided on each request for access (see Figure 6).

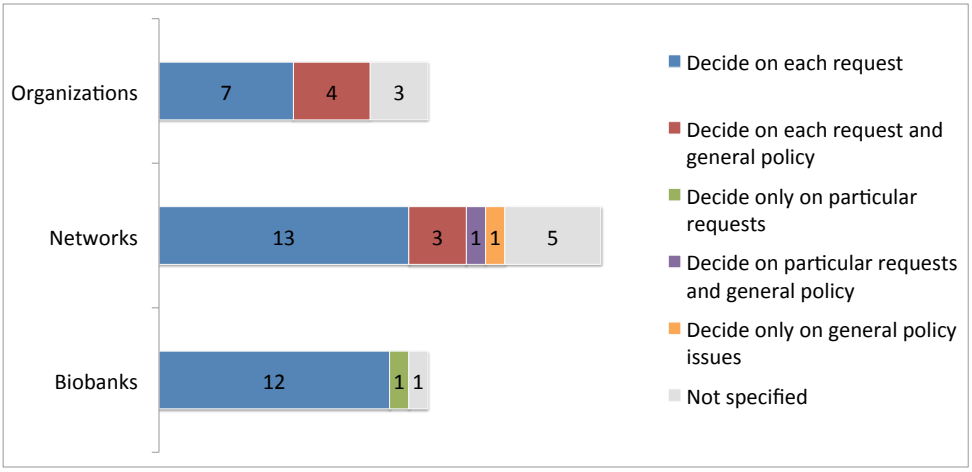

Figure 6: Mandate of access committee

3.5 Screening of scientific merits

The comparative analysis revealed that only half of the access arrangements (access arrangements of 11 organizations, 18 biobank networks and 11 biobanks (see Figure 7)) stipulate explicitly whether the scientific merit of access requests is screened. One organization's access arrangement stated explicitly that it did not screen the scientific merits, since it did not feel competent to conduct such screening. Access arrangements of 8 organizations explicitly provided a more extensive scientific screening, while only 4 biobanks and no biobank network provided such extensive screening.

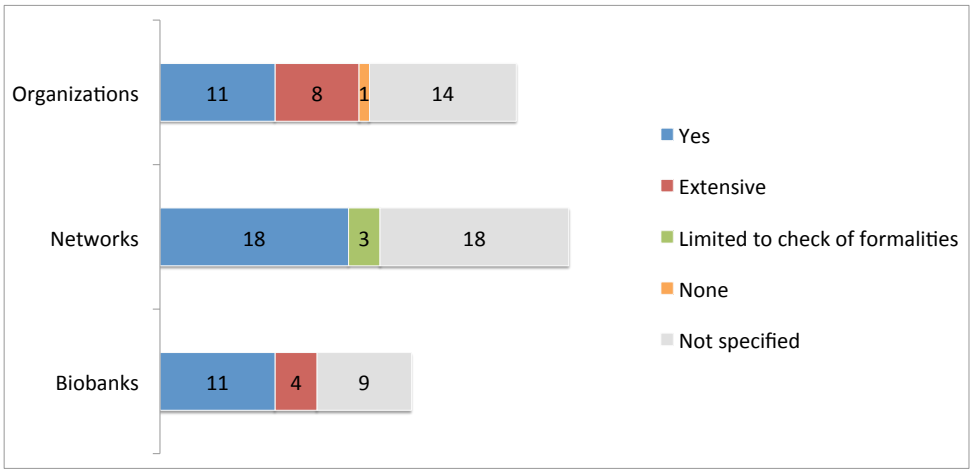

Figure 7: Scientific screening of access requests

3.6 Sharing or returning of research results

Access arrangements of 14 organizations, 17 biobank networks and 15 biobanks (see Figure 8) stipulated explicitly the obligation to share and/or return research data or results. When focusing at biobanks considered as population-based, one noticed that 9 out of 10 access arrangements provide for an obligation to share or return research data or results.

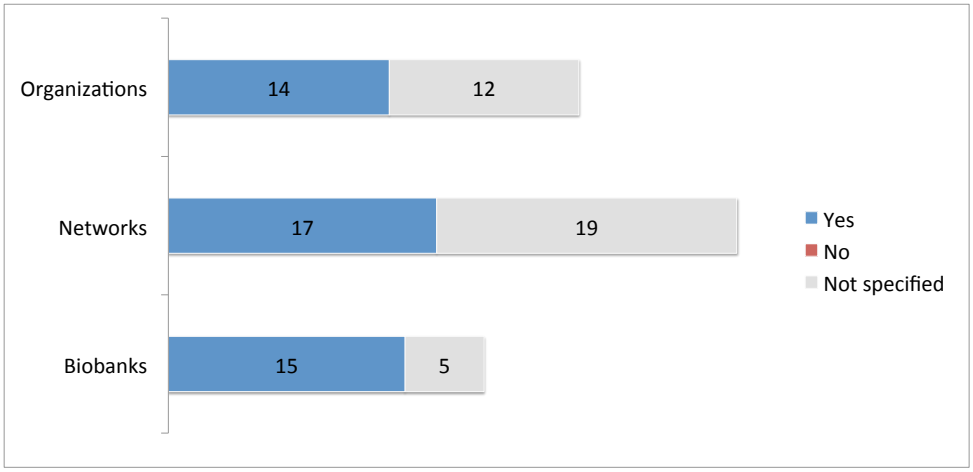

Figure 8: Sharing of research results

4 Discussion

The comparative analysis provides empirical data on 21 selected conditions characterizing access arrangements for biobanks. It covers access arrangements developed by 26 organizations, 36 biobank networks and 20 biobanks worldwide. Since we did not find evidence of trends or differences that specifically pertain to one of the three categories of biobank initiatives (i.e. organizations, biobank networks or biobanks), this section discusses trends and differences in access arrangements for the three categories together.

4.1 Lack of clear information

An important number of access arrangements does not contain (clear) information on how the concerned biobank initiatives define several of the 21 access conditions investigated in the current study. Such lack of information constitutes an important barrier for researchers who apply for access to biobanks (14,16,63,69,77,81,82,84,91).

4.2 Ownership or custodianship

The study revealed that the majority of the access arrangements do not stipulate anything in relation to ownership of HBM and associated data. This is probably due to the fact that it remains uncertain which 'ownership' rights can be held or claimed in relation to HBMs (14,23,69,83,84,92). Opinions in scientific literature differ on whether such rights can be held by the donor, the collector of HBM, the researcher using the HBM or a biobank (14,70,91–94)

Taken into account the uncertain status of 'ownership' on HBM, we suggest to focus instead on the (bundle/compilation of) rights held by the custodian HBM or data – irrespective of the question whether such rights could be considered as 'ownership' rights (2). B. Björkman pointed out that rights on HBMs could be constructed in many different ways depending on the legal relations included in the bundle of rights. She argued that the most important question concerns the determination of the rights to be included in such bundle. The question of whether such bundle of rights would constitute ownership is – according to B. Björkman and the PhD candidate – of minor importance (95).

It appeared from the comparative analysis that access arrangements contain different definitions of the rights and obligations of custodians (see section 3.3). Therefore, it remains – unfortunately – difficult for an applicant to know which rights a custodian holds over a collection of HBMs and data.

4.3 Level of custodianship: biobank vs. principal investigator

The results revealed a shift to provide custodianship of HBM and data to the biobank or biobank network and no longer to principal investigators. This shift is presumably due to the fact that biobanks increasingly store high numbers of HBMs and/or data, which cannot be managed in an optimal manner by an individual researcher/collector (23,65,81,91). One might argue that custodianship at the level of the biobank or biobank network can facilitate access to HBM and data, since it would no longer be necessary to obtain approval of each individual researcher or collector.

4.4 Level of custodianship of HBM: biobank network vs. biobank

Some of the studied access arrangements provide custodianship of HBM at the level of the biobank network, while the majority provides custodianship at the level of the biobank. The different approaches might be due to the fact that some collections were created as collaborative efforts within the framework of a biobank network; in which case the participating biobanks might be more willing to allow the biobank network to exercise custodianship. In other networks, the individual biobanks created collections of HBM and data outside the network and subsequently decided to share those collections in the framework of the biobank network. In this case, the individual biobanks might want to maintain the possibility to decide on access to 'their' HBMs and/or data. Both approaches can be defended, but an applicant needs be clearly informed on whether the biobank network or the biobank decides on access to samples and data.

4.5 Level of custodianship: data vs. HBM

The comparison demonstrated that custodianship of data (in contrast to custodianship of samples) is more often held at the level of biobank network. This might be explained by the fact that different researchers can access data simultaneously. Since the biobank maintains the possibility to access and use 'their' data, it might be more comfortable allowing the biobank network to decide which researchers can access the data shared in the network. The sharing of data could be facilitated by the fact that biobank networks decide on access to data and an applicant, therefore, needs to obtain authorization from fewer biobank initiatives.

4.6 Access committees

When biobank initiatives claim custodianship over HBM or data, they have the responsibility to develop transparent access arrangements and to establish access committees to decide on access requests. Such access committees need to ensure that HBM and data are used in accordance with the initial consent. They furthermore verify that the HBM is only used for research projects that demonstrate sufficient scientific merits. It is therefore no surprise that the comparative analysis confirmed that the majority of the access arrangements establish an access committee.

4.7 Screening of scientific merit and relevance

Only half of the studied access arrangements stipulate explicitly whether the scientific merit of access requests is screened. This is unfortunate, since applicants need to have clear information on such screening. Screening the scientific merits of applications can ensure that HBMs and data are not wasted (16). This is even more the case in relation to rare HBMs (81,96). Finally the biobank initiative might want to verify whether the proposed use of HBMs and data corresponds with the scientific aims of the collection (81).

Some biobank initiatives might not explicitly provide for the screening of the scientific merit of access requests, since they are of the opinion that such screening is the responsibility of an ethics review board or the organization funding the research project (69). Furthermore, access committees of biobank initiatives might not always have the capacity and/or specialization to screen the scientific merit of each application; especially in view of the wide range of disciplines of applicant researchers.

We recommend that clear information is provided to applicants on whether and how the scientific merit of their access requests is screened.

4.8 Obligation to share or return research results

The majority of the access arrangements require the returning and/or sharing of research results with the biobank or other researchers. This might be due to the fact that an increasing number of funding bodies require such sharing or returning of research results. Furthermore, this could be justified by the substantial (public) investment required to collect, store and manage in optimal manner HBM and data. However, the sharing or returning of research results is only useful, when the necessary capacity is available to store, correctly interpret and access the results.

Since researchers invest a considerable amount of time and effort in generating research results or data, they could be allowed – during a limited period of time – the exclusive right to decide who has access to them.

5 Conclusion

Several authors active in the biobank field pointed out that an increased level of harmonization of access conditions could facilitate access to biobanks (11,14,16,65,66,70,76,77,80). Since many access arrangements do not contain clear information in relation to several of these conditions, it is difficult to draw final conclusions on the extent of harmonization. We nevertheless wanted to provide some preliminary conclusions. First, we noticed that a number of access conditions (access to data and/or HBM (condition 1), type of HBM (condition 2), type of data (condition 3) and level of ownership (condition 4 & 5)) might not be considered as key conditions to determine the legal framework applicable to access to biobanks. It seems that access arrangements do not attach a lot of importance to those access conditions to determine how access to biobanks is regulated. Second, we noticed that a certain level of harmonization exists on the level of custodianship (condition 6 & 7), the establishment of an access committee (condition 8), the mandate of an access committee[31] (condition 9) and the sharing and returning of research results (condition 19). The comparative analysis demonstrated a lack of harmonization of access arrangements in relation to the other examined access conditions. Chapter 2 reports on an empirical study that shed more light on how access conditions are applied in practice. It focused on the evaluation of access requests, the right to decide on leftover HBM, the right to participate in benefits of scientific research and the obligation to share research results.

This could enable us to understand the lack of clear information and the lack of harmonization in relation to the majority of the key access conditions.

A complete harmonization of all access conditions might be not be feasible, considering the different nature of biobank initiatives and the different legal frameworks applicable to these initiatives (studied in Chapter 3) (1). A certain level of harmonization might, however, be reached on a number of key access conditions.

[31] The majority of the established access committees provide advice or decide on each request for access.

Chapter 2: Custodianship on HBM and data stored in biobanks

1 Introduction

Researchers need to be able to access efficiently different collections of HBM and data(69,97). However, biobanks and biobanks networks, as custodians of HBMs and associated data, need to exercise a certain control on access to and use of their collections in order to guarantee its long-time sustainability and the scientific, ethical and legal correctness of its use(1,16,69,93). In addition, custodians need to ensure that access requests comply with the applicable legislation and the conditions stipulated in the consent of the donors/patients(70,82). Balancing the rights and obligations of custodians, applicants and/or patients in relation to access to biobanks is of utmost importance to guarantee trust and confidence.

After many years of discussions there is still no answer to the question whether 'ownership' rights can be held or claimed in relation to HBMs (and associated data) collected for research purposes (14,23,69,83,84,92). Considering the uncertain status of 'ownership' on HBM, some suggested focusing instead on the concept of 'custodianship'(2), 'stewardship'(98) or charitable 'trust'(99). However, replacing the concept of ownership with new concepts does not automatically provide an answer to the practical question as to which rights and obligations can be held on HBM and data, as rightfully indicated by J. Conley e.a. (100).

R. Yassin *et al*. defined custodianship – in rather general way – as "*a caretaking obligation for biospecimens from initial collection to final dissemination of research findings"* (2)*,* but they did not define which specific rights and obligations the custodian holds on HBM or data.

According to the 'social constructivist theory'[32] "*ownership is the result of a series of social choices and events that could well have been different*." This theory does not aim to answer the absolute question whether a particular stakeholder – such as the custodian, the applicant or donor – can be the 'owner' of HBM. Instead, the theory considers it more useful to see ownership as bundles of rights and obligations of different stakeholders in relation to a particular object. This chapter studied the different perspectives of stakeholders in relation to the bundles of rights and obligations held by the custodian and the applicant in relation to access to HBM and associated data. The aim of the study was not to determine whether the custodian or the applicant should be considered as the 'owner' of HBM, since it appeared not possible to define the complete bundle of rights and obligations of both stakeholders.

Previous empirical research on biobanks focused on consent, public perception and participation in biobanks, etc. (56–59,61,62). Few research projects focus on custodianship of HBM stored in biobanks (11,17,101).

[32] Quigley, M. Property and the body: applying Honoré. *J MED ETHICS* **33,** 631–4 (2007).
28; Björkman, B. Different types--different rights. Distinguishing between different perspectives on ownership of biological material. *Science and engineering ethics* **13,** 221–33 (2007)

The qualitative study described in this paper, looked into the following research questions:
What are the different perspectives held by stakeholders in relation to the (bundle of) rights and obligations held by the custodian[33] and the researcher[34] applying for access to HBM and data?

Which topics divide the different stakeholders, when one tries to determine the (bundle of) rights and obligations held by the custodian and the applicant?

2 Methods

Data were collected via key informant, face-to-face (and some Skype) interviews. The aim of the interviews was to gain an in-depth understanding on how access arrangements are applied in the daily practice of biobanks and biobank networks. We also wanted to collect data on the hopes and concerns of the different stakeholders in this respect[35]. A qualitative research method was chosen to gather information on practical experiences and personal opinions of informants rather than factual information. Semi-structured interviews were conducted to collect information about a number of pre-defined topics (enlisted in the interview guide (Annex 3), but also to allow the interviewers to probe deeper when required. In addition, the interviews allowed us to validate the answers with the interviewees, reducing potential misunderstandings. That is why interviews were preferred above questionnaires. At the start of each interview the interviewers briefly explained the context of the study. This was done in such way as to not influence how the informants responded to the questions. The interview questions deliberately did not explicitly refer to legal concepts such as rights and obligations, in order to avoid that the informants would focus their answer on such concepts.

2.1 Interview guide

The topics of the interview guide (Annex 3) were determined on the basis of the results of the comparative analysis of access arrangements (Chapter 1) and a literature review on access to HBMs or data. The interview guide consisted of 8 structured, open questions. The interviewers used a pre-defined set of questions to be able to compare the answers of the different informants. The informants were first asked to explain their professional relationship and experiences with biobanking (Q1). A first topic related to the question how biobanks and biobank networks handle requests for access to HBM and data (Q2). After all, a lot of access arrangements studied in a previous comparative analysis (Chapter 1) did not define the specific mandate of access committees. A next topic touched upon the question whether different conditions apply for access to HBM and access to data (Q3). The majority of the interviewees did not attach much importance to the distinction between both. The question was

[33] The custodian is defined – by the authors – as the person(s) – such as the biobank manager of the access committee – and/or institution that exercises custodianship on HBM and data stored in a particular biobank.
[34] The term 'researcher' refers to researchers from the public and private sector.
[35] During the conduct of the interviews and the subsequent analysis, it appeared rather difficult to distinguish whether the informants were providing information about how custodianship works in daily practice or whether they expressed their opinions, hopes and concerns about how it should work. To the extent possible we used the verbs 'should' or 'could' in the result section to indicate when we refer to opinions, hopes and concerns of stakeholders rather than the current state of affairs.

therefore not longer raised in subsequent interviews. The third topic related to the question why biobanks and biobank networks develop different policies in relation to the return or destruction of leftover HBM (Q4). A fourth topic was the sharing of benefits. Several organizations suggest that a policy should be developed regarding the sharing of benefits of biobank research. However, the majority of biobanks and biobank networks do not provide anything in this respect. Prior to asking informants about their experiences and personal opinions on benefit sharing, the general question was posed what kind of benefits may accrue from using HBM and data (Q5). The question was posed in a general way in order to avoid suggesting particular types of benefits and benefit sharing, such as IPRs on HBM and data. Some informants suggested that returning and sharing 'research results' could be an example of benefit sharing. If this was not the case, the interviewers specifically inquired about the experiences and personal opinions of the informants on the return and sharing of research results (Q6). One of the informants suggested that information on which applicants are granted access to HBM and/or associated data in the framework of a particular research projects should be publicly available (Q7). Finally the topic was raised whether (publicly funded) biobanks and biobank networks should allow industrial companies access to their collections of HBM and data (Q 8). At the end of the interview the informants were given the opportunity to discuss ideas or concerns regarding access to biobanks that had not been discussed in the interview.

2.2 Data collection: Key informant interviews

2.2.1 Sampling strategy for the key informant interviews

Twenty-eight informants in Europe were selected by means of 'purposeful/purposive' sampling(102,103) and snowball sampling based on the information provided by previous informants. These sampling technics were chosen to capture the different perspectives of 7 types of stakeholders[36] – in particular (i) custodians of biobanks, (ii) representatives of biobank networks, (iii) clinical, (iv) academic and (v) industrial (research) applicants, (vi) patient representatives and (vii) representatives of industry –. We also conducted interviews with legal, ethical and biomedical experts (see Figure 9). The interviews with the 7 types of stakeholders enabled us to acquire a deeper knowledge of the current practices applied in biobanks and biobank networks and HBM research in general. Interviewing legal, ethical and biomedical experts provided a more in-depth understanding of the (ethical, legal and scientific) background and context wherein biobanks operate.

[36] Some of the informants fulfilled a double role, such as applicant and representative of stakeholders within an access committee. The interviewers considered those double roles in the analysis, but focused on the main role of the informant.

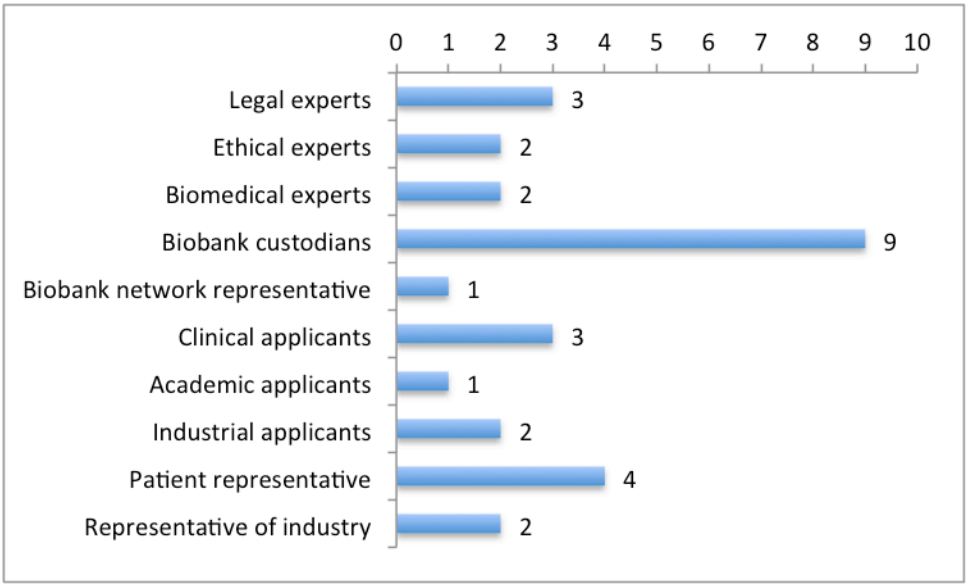

Figure 9 Distribution of informants per type of stakeholder or expert

We wanted to study variations in perspectives between the different types of stakeholders and experts in relation to the rights and obligations held by the custodian and the researcher/applicant. That is why we attempted to select at least two informants to represent each type of stakeholders and experts[37] [38].

During the analysis of the interviews, however, we discovered fewer variations in opinions than we would have expected. We also noticed that specific variations of opinions could not be contributed to specific types of stakeholders or experts. Informants who represent the same types of stakeholders or experts expressed as much variation in their opinions as informants who belonged to different types of stakeholders or experts. That is why we decided not to describe separately opinions per type of stakeholder or expert. Contributing variations of opinions to particular types of stakeholders or experts – instead of individual informants – could have distorted the representation of the results, since most variations were not linked to particular types of stakeholders or experts.

That we discovered fewer variations than we expected, might be due to the fact that some of the topics discussed during the interview were relatively new for some informants. For instance, some informants explicitly mentioned that they did not yet have a fully developed opinion on the right to share in benefits, the obligation to share research results and IPRs. It might also be due to the fact that we were only able to interview 28 informants. It would be interesting to interview more informants to discover more variations in opinions. However, it was not possible to interview additional informants due to time constraints.

[37] We were unfortunately only able to interview one informant representing a biobank network. The other selected informant in this respect informed us during the interview that he would rather answer the questions as custodian of a biobank and not as representative of a biobank network.
[38] We only interviewed one purely 'academic' applicant, since the majority of the applicants that we contacted, can be considered as both academic and clinical applicants.

2.2.2 Pilot interviews

The data collection started with pilot interviews with 3 informants. These were, in particular, (a) an academic bioethicist previously involved in research projects on biobanking; (b) a legal advisor on biobank projects, legislation and policies; and (c) a custodian of a biobank. The pilot interviews allowed to validate the interview guide (Annex 3) and to acquire first insights on the most important topics in relation to the rights and obligations held by the custodian and the applicant in relation to access to HBM and data.

2.2.3 Geographical scope of the interviews

Between October 2013 and January 2014 21 informants were interviewed in the Benelux. Informants were chosen in the Netherlands and Luxemburg because both these countries host ambitious national biobank initiatives such as the Parelsnoer Institute, BBMRI.NL, LifeLines in the Netherlands and Integrated BioBank of Luxemburg (IBBL). In February and March 2014 interviews were conducted with five informants in Denmark, Sweden and Norway (see Figure 10). The interviewers chose to compare the Benelux with the Scandinavian countries because the latter are considered pioneers in the development of biobanks and biobanks networks and in epidemiologic research(32). This pioneering role is, amongst others, due to the fact that these countries have a long tradition in storing HBM and health data of patients/donors in the framework of health care services and population-based studies. An interesting dimension of the Swedish biobank landscape is the well-documented cooperation between university biobanks and pharmaceutical companies, such as AstraZeneca and Pfizer. Additionally a representative of an Italian patient organization was interviewed, since this organization represented patients with a rare disease. We combined the interviews with on-site visits of biobanks in Belgium, Denmark and Sweden to observe their existing policy and practices in relation to access to biobanks.

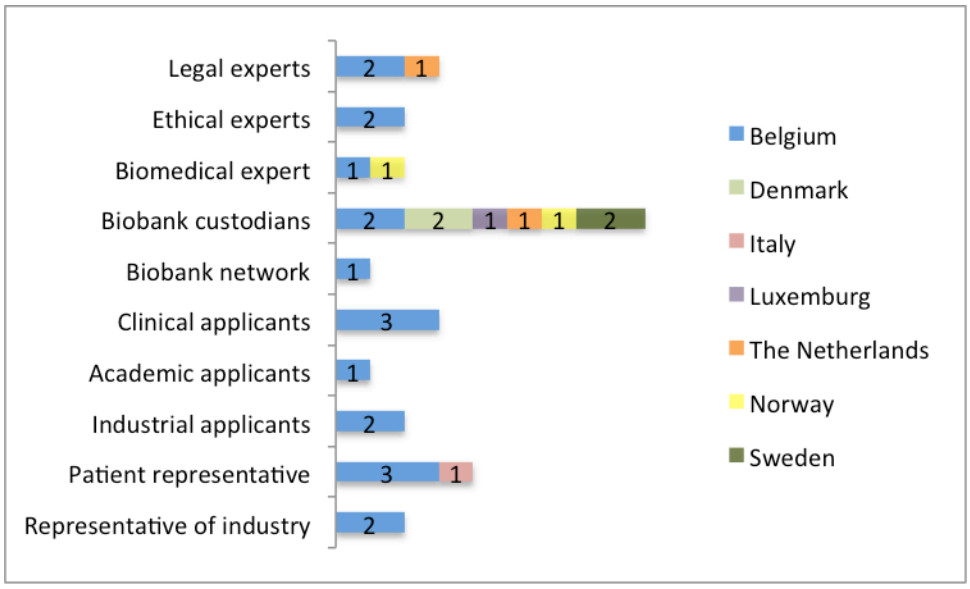

Figure 10 Geographical distribution of stakeholders and experts[39]

2.2.4 Interviews

The interviews were recorded and entirely transcribed *ad verbatim*. For each interview, a short report was created about the context and the interviewee's characteristics. The interview data are handled with confidentiality and the informants' identity remains anonymous in reports and publications accruing from the study.

2.3 Data analysis of the interviews

The data analysis phase consisted of an inductive analysis according to the Qualitative Analysis Guide of Leuven (QUAGOL)(104).

First, the transcriptions of the interviews were thoroughly reread by two members of the research team to familiarize themselves with the data and to get a sense of the interview as a whole. During the reading process, the key phrases were underlined. Thoughts or reflections evoked in some passages were noted in margins. Secondly, a narrative interview report was drafted in order to articulate the essence of the interviewee's story in answer to the research questions. This resulted in a brief abstract of the key storylines, including a summary impression of the characteristics of each interview. In a third stage, conceptual interview schemes were created. Those schemes provide an overview of the concepts that appear relevant to get an insight into the research topic. In the fourth stage, the interviews were reread to verify whether the content of the conceptual interview schemes reflected the most important concepts aimed at in the research questions. This enabled us to adapt, complete and refine the conceptual interview schemes. The fifth stage consisted of a comparison of the conceptual interview schemes of the different interviews to identify and adjust common themes, concepts or hypotheses.

[39] One informant was active in two different countries

The actual coding process started with the drawing up of a common list of concepts (see Annex 4) (stage six). This was done without imposing a hierarchical order and based on conceptual interview schemes. The research team evaluated and discussed the list of concepts. Overlap or vagueness was remedied by mutual consensus. The resulting list of concepts was introduced as preliminary codes in the software program 'Dedoose'[40]. In the seventh stage, each interview was read again with the list of concepts/codes at hand. Each significant passage of the interview was linked to one of the concepts/codes of the list. If a particular passage in a particular interview could not be linked to a specific concept, the list of concepts was adapted. In stage eight, every concept was analysed through a careful exploration and study of all citations associated with each concept. The researchers tried to understand and articulate the meaning of the concepts in their own words. The ninth stage consisted of the extraction of the essential structure of all the interview data. Starting from the conceptual interview schemes of all interviews, the researchers formulated a conceptual framework that organizes and structures all concepts in a meaningful way. Based on the conceptual framework (stage 9) and the in-depth analysis (stage 8), the researchers were able to systematically and carefully describe essential findings in answer to the research questions. Significant quotes were added where necessary and relevant. Finally, a formal peer debriefing with the other members of the research team was conducted to discuss and check the results in answer to the research questions.

3 Results

3.1 Evaluation of access requests and decision on access to HBM and data

3.1.1 Which committee or body should evaluate access requests?

During the interviews the question arose to which extent access committees should evaluate access requests, when an ethics committee also evaluates the research project. Some informants were in favour of the idea that only an ethics committee should make such evaluation. In their opinion, the role of the access committee should be limited to questions related to the availability and suitability of HBM and data for the research project. The majority of the informants felt that the access committee could also evaluate the quality and/or usefulness of the research proposed in the access request.

In this respect a custodian of a biobank in the Benelux stated the following:

> "The medical ethics committee is according to me not capable to evaluate the scientific part. It can evaluate whether something is ethical acceptable; that is why they are there, but not to evaluate the scientific content. (…) They are not equipped for it. Because every time you have a new specialisation, you need new expertise … this is also why we have stakeholders[41]."

[40] http://www.dedoose.com/

[41] Translation by the authors of the following excerpt in Dutch: "*De medische ethische commissie is volgens mij niet in staat om over het wetenschappelijke deel te oordelen. Ze kan wel oordelen of iets ethisch verantwoord gaat, daar zitten ze ook voor, maar niet om een wetenschappelijke inhoud te gaan beoordelen. (…) daar zijn ze niet voor toegerust. Want dan moet je iedere keer voor ieder specialisme, moet je dan toch de kennis hebben…Dat is ook waarom we stakeholders willen hebben.*"

Some informants stressed the importance of an increased interaction and collaboration between the access committee and the ethics committee (and possible also the funding body) in the evaluation of an access request.

Several informants stressed that the access committee and/or an ethics committee should avail themselves of the necessary expertise and experience to evaluate access requests. They questioned whether this was always the case. If one access committee is established for the entire collection of HBM and data from a particular institute, such access committee should comprise representatives from different medical disciplines (such as pathology, surgery) as well as clinicians that collected HBM and data for the biobank, patient representatives and legal, ethical and biomedical experts.

Some informants suggested that external experts could or should be consulted in case the access committee does not have access to the necessary expertise and experience to evaluate an access request.

Another important requirement advanced by the informants is the need for profound guarantees that the committee or body that evaluates access requests can act sufficiently independent from the researcher/principle investigator that requests access to HBM and data from the biobank. Such independence could be ascertained by involving one or more external experts in the evaluation of access requests[42].

3.1.2 Which criteria should be applied in the evaluation of access requests?

Most informants felt that the evaluation of an access request should not be limited to the verification of administrative formalities. The most important criteria suggested by the informants during the interviews related to (1) the availability and suitability of HBM and data for the proposed research project; (2) the quality and scientific value of project; (3) the scientific, societal or medical usefulness of the project; (4) the research merits of the applicant; (5) the ethical value of the access request; (6) the priorities of the biobank; (7) whether the requested HBM is rare (see Table 2). Several informants mentioned that only the access committee disposes of the required information on the collection of HBM and data to evaluate the first criteria.

The majority of the informants suggested that one should evaluate the quality and/or scientific value of a research project. Such evaluation will take into account whether the research question and hypothesis, the research method and the study design are solid. The evaluation will also check whether it can lead to valid and reliable results. It should furthermore look into the feasibility of the study and the chances of a successful outcome. Another question that should be assessed, in order to avoid under- or overpowering of the study, is whether the requested amount of HBM and data is statistically significant to obtain relevant results.

[42] One should, however, make sure that no conflict of interest exists, when such external experts evaluate access request.

According to the informants, an access request may also be evaluated on its scientific, societal or medical usefulness. This could be related to the question whether the suggested project (i) contributes to the improvement and/or accessibility of health care (in particular clinical practice, treatment, survival, quality of life); (ii) corresponds to a high medical need; (iii) differs from previous research; (iv) adds value to the existing state of the art; and (v) leads to new (scientific) insights or outcome. Several informants commented that it might be difficult to (objectively) predict the outcome of proposed research projects and whether a future research project would use HBM and data in a more useful way. They therefore suggested that one should not be too strict in evaluating the usefulness of a research project, when the evaluation of the other criteria is positive.

In this respect, a representative of industrial applicants in the Benelux stated the following:

> " Nobody can predict the future to foresee whether we will receive within 6 months … a research application that is more relevant in relation to the (useful) knowledge that it will provide us. (…); Such request might never come and in this case you possibly deny access to a valuable project. So, I think it constitutes an important responsibility and a difficult exercise. (…) If all evaluation criteria are positive, I feel that one should move ahead (with the project).[43]"

In their evaluation of access requests, the informants attach quite some importance to the expertise, experience, research merit and/or credibility of the applicants and their research group and/or research institute. In this respect, the informants suggest that one could take into account the track record, publications and previous research projects of the applicants, their research group and/or research institute. They furthermore suggested taking into consideration the fact that the applicant is affiliated to a renowned institute/research group or an institute that disposes of excellent research facilities. However some informants commented that it could be quite difficult to objectively evaluate this aspect, since one needs to dispose of the necessary scientific knowledge and expertise in the particular domain of the application. Several informants mentioned that within a particular research field or country, access committees, ethics committees, researchers/PI and research institutes know each other and their merits and that therefore access request of known researchers or research institutes could be dealt with more favourably. It therefore appears difficult to evaluate access requests in a completely neutral manner. Two informants suggested creating an accreditation system/research passport for researchers. This could enhance transparency and trust and rule out that the evaluation of the research merits has to be repeated for every new access request. It remained unclear, however, which institute or organization could develop such accreditation system or research passport.

[43] Translation by the authors of the following excerpt in Dutch:: "*Niemand heeft een glazen bol natuurlijk om te zien van "oké, misschien gaan we binnen 6 maanden (…) een onderzoeksaanvraag krijgen die ons qua informatie dat het project gaat opleveren, nog veel relevanter is. (…) mogelijks komt die vraag er ook nooit en dan ontzeg je een mogelijk ook heel waardevol project toegang. Dus ik denk dat dat een heel belangrijke verantwoordelijkheid is maar ook een heel moeilijke oefening. (…) Als alle evaluatie-criteria positief zijn, dan vind ik dat je er ook voor moet gaan. (…).*"

Another dimension described by the informants is the so-called “ethical value” of an access request. This implies that the access committee would verify whether the research use, as described in the access requests, corresponds to the informed consent and/or ethical approval that were obtained in relation to the requested HBM and data[44]. Secondly, the applicant may be evaluated on the measures it will take to protect the personal data of the donors.

Several informants indicated that many of the existing biobanks focus their collection of HBM and data on certain pathologies. That is why, according to some of the interviewees, it is not unusual that priority is given to research that corresponds to the mission or focus of the biobank or the (research) strategy of the research institute or company, such as a particular disease. It was stated that biobanks might also prioritize research request that relate to health care priorities of their country of origin. The biobank may also limit access to HBM and data collected in the framework of prospective studies or clinical trials.

Several informants suggested that a biobank could be stricter in evaluating requests for access to rare HBM, such as for example brain tissue. While some types of HBM are clearly rare, it may not always be easy to make a distinction between ‘rare’ and ‘commonly available’ HBM.

Table 2 Overview of evaluation criteria suggested by informants[45]

1. Availability and suitability of HBM and data
2. Quality and scientific value of project
    i. Research question, hypothesis, method and study design
    ii. Possibility of valid and reliable results
    iii. Feasibility of study and chances of successful outcome
    iv. Statistical significance of requested amount
3. Scientific, societal or medical usefulness of project
    i. Contribution to improvement and accessibility of health care
    ii. Corresponds to high medical need
    iii. Differs from previous research
    iv. Adds value to state of the art
    v. New (scientific) insights or outcome
4. Research merits of applicants
    i. Expertise and experience of applicants
    ii. Credibility of applicants
    iii. Affiliation with renowned institute/research group
5. Ethical value of access request
    i. Corresponds to informed consent
    ii. Corresponds to ethical approval
    iii. Sufficient measures to protect personal data
6. Priorities of biobank
7. Rare or common HBM

[45] This overview does not provide all possible evaluation criteria. There might be an overlap between some of the evaluation criteria.

Two informants, with a legal background, pointed to an extra dimension: the legal nature of the evaluation criteria to allow access to HBM and data. First of all, they posed the question to which extent the biobank could exercise a discretionary power to decide on access requests and whether some or all of the evaluation criteria should be determined by the national legislator. They highlighted the importance of motivating the decision on access. They stressed the fact that equitable and proportionate sets of access criteria should be provided. The criteria should be applied in a non-discriminatory, objective and transparent manner. They also suggested that some kind of appeal body should verify whether the access committee respected the conditions determined by the legislator and/or the procedural criteria in relation to the motivation and the evaluation of the access request. All informants seemed to agree that no different evaluation criteria should apply for academic and non-academic applicants and between external applicants and applicants affiliated to the biobank. They did feel that different access fees could be justified (see hereunder).

3.1.3 Motivation of access requests

All informants agreed that the applicant could have legitimate interest to protect the confidentiality of some information. They all agreed that he should therefore not provide all details of the research project in the access request. Several informants pointed out that the information to be provided in the access request is, to a large extent, determined by the criteria used to evaluate the access request. It appeared difficult to reach a consensus on which information should be made available to the committee or body that evaluates the access request. Informants mentioned that no guidelines are available in this respect. One informant referred to the Good Clinical Practices (GCP) that provides guidance on which information needs to be provided in a protocol in the framework of a clinical study. Since the GCP were developed in a clinical context, some of the information will not be useful for use of HBM and data in research projects. The information to be provided could be different depending on the type of research.

A topic raised during the interviews is to which extent the applicant should specify which type of research would be conducted. One informant representing an industrial applicant felt that it should be sufficient to indicate that the HBM and data will be used for scientific research or research and development and not for diagnostic or therapeutic purposes. If necessary, he felt, the type of research in wide pharmacologic terms, such as neuroscience or virology could be added. Other informants suggested that the applicant should provide more specific information on the type of research.

A further topic was how much information applicants should provide on their research project in the access request. Most informants felt that the applicant should provide a short synopsis of the research project. This synopsis could be supplemented with a more elaborated description of the research question or hypothesis and the scientific, societal and/or medical objectives of the project. This description would enable the access committee or ethical committee to evaluate whether the research project complies with the informed consent and the ethical approval of the research project. They could further check whether it complies with the notification of the activities and aims of the biobank to the ethical committee and the national agencies for medicinal products, such as the FAGG (Belgium),

as provided in the future article 22 § 1 of the Belgian Act on HBM[46]. One informant raised the question whether it would be sufficient if the applicant confirmed that the research project complies with the ethical approval and the informed consent. In this case the custodian would not further verify such compliance.

The majority of the informants suggested that the applicant should describe – in more or less details – his research methods and/or study design to evaluate the quality of the research project and the chances of successful outcome of the project. Some informants highlighted that it may be difficult to predict the research methods that will be used, since these could evolve in the course of the project. This would be especially the case for prospective studies.

Some informants suggested that the applicant could be required to provide a technical motivation of the (statistical) relevance of the requested amount, the sample size and the specific type of HBM and data. This could, for example be the use of HBM and data from specific groups of patients and fresh HBM. The more elaborated outline of the research project could also contain a description and/or motivation of the additional medical or biomedical data that the applicant wants to use in the research project.

3.2 Decision on fate of leftover HBM at end of project

Most informants felt that the custodian of the biobank and the applicant have to agree upon the return and/or destruction of the leftover HBM before the applicant is granted access to the HBM and data. Alternatively the access policy of the biobank could contain general rules on leftover HBM; however several informants considered it difficult to determine in general whether one should return or destroy leftover HBM after the research project. They felt that such decision should be taken on a case-to-case basis. Informants suggested, as first criterion for deciding on the return or the destruction of leftover HBM is the type of HBM. Some HBM, such as serum, is much more vulnerable to quality changes than others, such as DNA. Another criterion relates to the question whether the type of HBM used in the project is rare or can be recollected relatively easily. One could also take into account the amount of leftover HBM after the end of the project, since it may not be worth the effort to request the return of small amounts of HBM. All informants agreed that the most important criterion is the quality of the leftover HBM and the extent to which the HBM can be re-used in a new research project. Quite some informants expressed concern that the biobank cannot have sufficient control on how the applicant stored the HBM and how often and under which circumstances frozen HBM had been thawed. If HBM is not managed in a proper way, it could pollute the collection of HBM and data of the biobank. It could also have an important impact on the quality/credibility of future research with leftover HBM. Some custodians only allow the return of leftover HBM and data in the biobank in case of previous experiences and/or collaborations with the applicants. A number of informants mentioned that the cost and complexity of the return of leftover HBM could be a factor to decide on whether or not to have HBM returned. Several informants are in favour of a trend to share HBM only between

[46] Act of 19 December 2009 concerning the obtaining and use of human biological material for medicial applications on human beings and for research purposes (Act on use of HBM), as modified by the act of 23 December 2009, 19 March 2013 and 30 April 2014.

biobanks and not to provide them directly to individual researchers, since the exclusive exchange between biobanks would increase the chances that the HBM and data is stored in a proper way. However, some individual researchers are not affiliated to an institution that hosts a biobank.

Table 3 Overview of criteria suggested by informants to decide on leftover HBM

Type of HBM
Rare or common HBM
Amount of leftover HBM
Quality and reusability of leftover HBM
Previous experiences and/or collaborations
Cost and complexity of return

A related question is whether the applicant could use the leftover HBM and data in new or follow-up research projects. The majority of the informants pointed out that applicants are only granted access for a limited period of time and for research use specified in the access request. That is why the applicant should certainly inform the access committee and/or the ethics committee of the fact that HBM is left over and that he wants to use this HBM for a new purpose. Most informants felt that the applicant could only use leftover HBM in a new or follow-up project after submitting a new request or an amendment to the initial request. The access committee or ethics committee should then approve such amendment. An amendment to the initial request could suffice, if the new project falls within or is closely related to the scope of the initial research project. Regarding this, the informants referred to the fact that similar rules are applicable in relation to the approval of research projects by ethics committees. Since, at this stage, the applicant has already been evaluated, several custodians stated they are relatively flexible in the evaluation of the new use of leftover HBM. All informants agreed with the possibility to stipulate in the access arrangements the prohibition to transfer the HBM and/or data to third parties without permission of the biobank. One informant suggested that the initial application could already describe additional research hypothesis or methods that could be used if the initial ones did not work. This would have the advantage that such alternatives would already have been approved.

Some informants were sceptical about the possibility to verify whether the applicant had returned or destroyed all leftover HBM. They pointed out that it would be very burdensome and difficult – or impossible – to verify whether the applicant still has some of the HBM stored in his facilities. That is why it was argued that the return (or destruction) should be the exceptional situation. Biobanks should – to the extent possible – divide HBM in different aliquots and provide only the minimum amounts of HBM that is statistically relevant to obtain a successful outcome. Additional amounts of HBM could be provided in the course of the project.

Table 4 Level of consensus on fate of leftover HBM

Return or destruction	No consensus
Re-use	Approval of access committee (and REC)
Transfer to third party	Approval of access committee (and REC)

3.3 Participation in benefits of research project

The informants were asked whether it would be desirable that some of the financial or non-financial benefits obtained from the results of the research projects would be shared with the biobank and the community at large. Several informants pointed out that a lot of different stakeholders – such as researchers from different disciplines, funding agencies, donors or developers of research tools – contribute to research projects. This makes it very difficult to predict in advance or evaluate at the end the importance of different contributions for the final result/outcome. One informant mentioned that the contribution of HBM and data in the creation of benefits can be very long term and uncertain. That is why several informants mentioned that it could be very burdensome or even impossible to grant every contributor a certain – even small – percentage in the financial or non-financial benefits of research projects. Quite some informants did, however, argue in favour of developing ways to feed some of the benefits back into the biobank infrastructure.

In this respect, a custodian of a biobank in Scandinavia stated the following:

> "*So we should be able to find ways of feeding some of the benefit back into the infrastructure, but not to make a profit (…). But I think it's highly justifiable that some of the financial benefit that comes out of research based on biobanking should be fed back into the infrastructure, just like you use some of your profit in a company to feed back into development."*
>
> *"I'll never be able to cover total costs, so I need to get money from central sources, and that's where I would want some kind of public sector, health-economic analysis and mechanism to feed some of the benefit back in. Because if we do it right, there are big winnings for healthcare authorities.*"
>
> "*It's the same with the development of vaccines against human papilloma virus. (…) Some of these benefits take a long time to work through (…) It's nevertheless there and there must be economic models that help you calculate it or plan investment. (…) Make no mistake, that impact of HPV vaccine would not have happened at that speed without biobanks.*"

One informant observed that the initial contractual agreement should clearly define – prior to the beginning of the research project – if and under which conditions one may participate in the benefits of a research project. This prior agreement should then also specify who will be able to use the research results and for which purpose.

The next question was which criteria should apply to determine which contributors could participate in the benefits from a research project making use of HBM and data from a biobank. In answer, most informants referred to the (scientific) contribution of the different stakeholders in a research project. There was a consensus that the mere delivery of HBM is insufficient to participate in the benefits of a research project. Nonetheless, everybody agreed that one should be compensated for the costs of collecting, storing and providing HBM and data to the research project. Possible scientific contributions to a research project mentioned during the interviews were (a) an inventive step; (b) participation or advice in the development of the research hypothesis or method or execution of research project; (c) advice on the optimal selection and use of HBM and data to respond to a particular research question; (d) the initial idea or initiative to collect a particular type of HBM and/data; (e) the creation of a collections of HBM; (f) an extensive characterisation of HBM; (g) the development of modified HBM

(such as cell lines, plasmids); and/or (h) the preparation and cleaning up of data sets. Several informants mentioned that, in case it wants to participate in the benefits, the biobank could position itself more as a partner in research projects and not merely as supplier of HBM and data.

The interviews also dug deeper into the informant's opinions about possible mechanisms to share benefits of research projects with the biobank or the public at large. It became quite clear that most informants were rather sceptical about the idea that the biobank or the collectors of HBM and data would hold intellectual property rights (IPRs) on the research results. Nor did they think that the biobank or the collectors of HBM and data should receive royalties in relation to the exploitation of such IPRs.

A custodian from a biobank in Scandinavia – with previous experience in the pharmaceutical industry – stated the following in this respect:

> "*For me, with my background, it's hard to see how a royalty mechanism would work. Even though biobanks have compressed the time taken to getting the value, it's still a long development time to get a drug to the market.*"

Most informants referred to the fact that biobanks charge a user or access fee. In the best-case scenario, this fee covers all development, investment and maintenance costs in relation to the creation of the collection of HBM and data. It also covers the provision of additional services, such as data management and analysis. An additional overhead is sometimes charged to guarantee the self-sustainability of the biobank and to enable the enhancement of its services to future applicants. One informant mentioned that organizations that fund biobank infrastructure, sometimes explicitly require that user fees should compensate part of the costs. Most informants indicated that biobanks currently often have problems to recover all costs via access fees. Nevertheless, they indicate that it is difficult to justify a combination of (higher) user fees and a participation – in term of rights or royalties – in the final results of research.

Most informants indicated that the same access conditions apply to all applicants. They did agree that different access/users fees for public and private or internal and external applicants could be justified by the fact that biobanks are mostly funded with public investments or by the research institution affiliated to biobank. Both (academic) custodians and (industrial) applicants indicated that an industrial applicant may prefer paying a higher, but all-inclusive access fee at the beginning of the project. In doing so, they would not have to negotiate about royalties at a later stage, when certain research results become commercially valuable. The applicant bears the risk of the research project being unsuccessful, but has certainty that he will not have to pay additional royalties later. Some informants suggested that such up-front payments could guarantee fewer conflicts and uncertainty later in the project.

A number of informants in Sweden, Norway and the Netherlands argued in favour of a public contribution fee that applicants would be required to pay to obtain the right to (commercially) exploit the potential benefits of their research project. The applicant would pay such an extra fee or tax for the use of a common good/infrastructure. Those fees would go into a central fund and could be allocated back into research (infrastructure), health surveys, and the improvement of public health care. The aim of such fee would not be to generate profits, but to provide a (fair) return for the contribution of the

common good/infrastructure after (possible) commercialisation of research projects. One informant made a parallel with the public contribution fee or tax charged for the exploitation of natural resources, such as gas fields.

Other benefit sharing mechanisms that were discussed were the BRIF (Bioresource Research Impact Factor) initiative[47], co-authorship or participation in the research project by the initial collector and the sharing of non-financial benefits with groups of patients (not individual patients) that donated HBM and data and mechanism to guarantee that health care improvements become available to patients.

3.4 Sharing research results

There seemed to be consensus amongst the informants that research results generated within publicly funded research projects should – under certain conditions mentioned above – become publicly available. The majority of the informants were in favour of the idea that the custodian would require the applicant to share the research results with the biobank and/or other researchers. Several informants suggested that it could be a way to maximize the use of HBM and data. This would certainly be the case for HBM and data that are quite rare or require a lot of effort or investment to collect and analyse, such as whole genome sequencing data. They felt that it would optimise the use of gained knowledge and expertise in relation to the collection of HBM and data. Some informants suggested to investigate the possibility to generate multipurpose data that would not only be useful for the applicant, but also in future research projects. Combining research results from different projects may speed up future research and avoid that particular research is conducted several times.

Another reason to require the sharing of research results is the possibility to enrich the collection of HBM and data. Such enrichment could be realized by obtaining additional information in relation to the HBM and data stored in the biobank and extending the characterization and understanding of HBM and data. Additional information on HBM and data could also be useful for the improvement of the quality of the collection of HBM and data. It could provide the access committee or the ethics committee with additional information to evaluate future access request. It could also allow future applicants to make more informed decisions on which HBM and data are optimal for their research project. Finally the biobank could use this information to target specific subgroup of donors for the collection of new data based on information from previous research projects.

Access to research results from previous projects could allow researchers from multiple disciplines and with different experiences to reinterpret and question the results. It would allow them to study the generated data from new entry points or perspectives while working on new research questions. This is particularly important since biomedical research increasingly depends on multidisciplinary approaches and no researcher or research institute can avail of all possible expertise.

[47] http://www.gen2phen.org/groups/brif-bio-resource-impact-factor

Finally the requirement to share research results corresponds with requests of an increasing number of scientific journals to deposit the raw data of publications in public databases to verify the quality of research and to avoid fraud. Furthermore, several funding agencies – such as NIH, Wellcome Trust and the Dutch cancer association “KWF Kankerbestrijding “ – require that the results of research projects are made publicly available.

Whether or not the researcher should share the research results with the biobank and other researchers is determined in the first place by what has been agreed upon in the access arrangement or in the material transfer agreement. Informants indicated that it is only useful to return research results, if the researcher can guarantee that the results have been managed in a proper way and that sufficient quality control has been conducted on the results. Without such guarantee, it could be dangerous and misleading to use results from previous research projects.

The majority of the informants highlighted that a biobank could only require the return of research results, if it disposes of sufficient infrastructure and resources not only to store the results, but also to make them available and allow other researchers to use the research results in future projects. Biobanks should furthermore have clear arrangements on who could access the results and under which conditions. They should have the necessary capacity to evaluate requests for access to research results. Some informants suggested that different levels of access could be provided to different stakeholders, such as biobanks, funding agencies and future researchers. Another possibility could be that third parties would only be granted access to a limited part of the research results. For example, the biobank would only access results that specifically pertain to the characterisation and quality of HBM, while researchers would only be allowed access to specific raw data that are relevant for their research. Some informants raised the question whether it is desirable or optimal that individual biobanks store all research results generated with their collection of HBM and data. A first suggestion was that specialized biobanks or biobank network with the necessary scientific expertise and knowledge may be more suited to store and provide access to the research results in a meaningful way. Another possibility would be that the researcher would only return metadata on research results to the biobank and that future researchers would be able to conduct queries in catalogues with such metadata. The research results could also be stored at the level of biobank networks or central research facilities, such as the European Genome-Phenome Archive (EGA).

Several informants pointed out that it could be difficult to correctly interpret research results without the necessary background and knowledge on how the research results have been generated.

In this respect, a custodian in Scandinavia remarked the following:

> “*Raw data can be so vast and enormous, and unless you understand how to interpret it, it can be just meaningless* ”

That is why several informants suggested involving the researcher that generated the research results in new research projects. After all, this researcher formulated the initial research hypothesis and developed the research protocol and could provide valuable information on how the research results have been obtained and how they can be interpreted and used in further research.

The majority of the informants agreed that the applicant who generated the research results, would only accept sharing research results if their legitimate interests were respected. The initial researcher could be given a preferential or priority right to use, publish or obtain IPRs in relation to the research results, for a certain period of time – for example 1,5 to 3 years – after the end of the research project. During this period of priority, other researchers could only access the results with the explicit agreement of the initial researcher. After this period the initial researcher maintains all rights to use his results and may require that he/she is informed and/or consulted when another researcher wants to use "his" research results (see hereunder).

The majority of the informants did express the opinion that the final decision to grant access to the research results should not be taken by the initial researcher, but rather by the access committee or the ethics committee. This was amongst other motivated by the fact that the initial researcher may have a conflict of interest, when having to decide whether a new research project – possibly in the same or similar research domain – could use his research results.

Finally the initial researcher may be entitled to a recognition and/or compensation for his/her investments in creating the research results and making them available to others. The biobank could motivate or suggest the new researcher, who requested access to research results, to discuss the possibility of collaboration with the initial researcher and/or co-authorship.

Another topic discussed during the interviews was whether one could make access to HBM and data dependent upon return of research results. Several informants supported such requirement, while others felt that it should be agreed on a case-to-case basis and such condition could not be mandatory.

The majority of the informants agreed that the publication of results of research involving HBM and/or data is insufficient to comply with the obligation to return or share the research. After all, very often only a limited selection of the research results is actually included in publications. Some informants were in favour of returning and/or sharing negative results of research projects.

3.5 Preferential or priority access to collection of HBM and data

A new topic that arose during the interviews was the fact that quite some collections of HBM and/or data are driven by specific research projects. These are created at the initiative of specific principle investigators or researchers.

Those principle investigators perhaps created a historical collection of HBM and data. They may have taken the initiative to start – in collaboration with the biobank – the collection of particular HBM and data for future research projects. This could be the case, when researchers applied for funding and want to make sure that they will have access to sufficient amounts of HBM and data to conduct their project.

Several informants suggested that a researcher that took such initiative could dispose of more rights on the collection of HBM and data, since the collection may not have existed without his/her initiative and/or contribution. First of all, this researcher could request and be granted a preferential or priority right to conduct research with the collected HBM and data and to publish the results. This priority right would of course not have an absolute character because the researchers will still need to comply with the informed consent and will need to obtain approval from an ethics committee. The biobank also

needs to have a clear policy on how it will evaluate a request to initiate a particular collection of HBM and data and a subsequent request to use the collection in a research project.

The right to decide whether and under which conditions other applicants can access the collection of HBM and data, may be partially and temporarily transferred to the principle investigator. This could imply that the principle investigator would be given – together with the biobank or alone – the "disposition right" over the HBM and data collected at his initiative. The disposition right, however, returns to the access committee after the expiration of the period of priority (or exclusivity or embargo), for example at the end of the project in the framework of which the HBM and data was collected.

Some biobanks provide a priority setting in their access policies between different types of applications and restrict access to HBM and data collected in the framework of prospective studies, longitudinal population based studies or clinical trials. Several informants considered it quite common that particular HBM and data are predisposed for specific research projects to ensure that sufficient amounts are available. Such predisposition is limited in time and will often only exist for the duration of the research project. It may furthermore be limited to a certain percentage of the available HBM and data.

3.6 Exclusive access to collection of HBM and data

The interviews revealed that none of the informants was in favour of the idea of granting applicants an exclusive right to use and exclude others from using particular types of HBM and data. Some argued that it would be unethical to allow such exclusive access. Several informants argued that exclusivity unnecessarily limits access to HBM and data and could slow down or hinder scientific research and the development of new scientific or medical knowledge. They furthermore shared the view that collections of HBM and data created with public funding should be accessible to all researchers.

3.7 Biobank as scientific partner or collaborator of a project

Several informants expressed the desire that in the future the biobank would become a scientific partner in research projects and would participate in the drafting of research protocols, the execution of research projects and the interpretation of research results. They feel that the role of biobanks should not be limited to the delivery of HBM and data. According to them, the biobank and the applicant could also share existing knowledge and expertise and clinical follow-up data. In this case both parties could conclude a collaboration agreement that goes beyond the mere regulation of use of HBM and data. Such agreement could also govern the provision of additional services (medical imaging, genetic sequencing), the rights and obligations of both parties in the research project and the sharing of benefits and co-authorship. Such a more elaborated collaboration could constitute an additional motivation for biobanks and collectors to collect and share HBM and data. Some informants suggested that it is easier to share HBM and data within existing (long-term) collaborations or consortia.

One of the informants stated the following in this respect:

> "*I participate now in a large consortium with pharmaceutical companies and they in fact make their samples easily available. They share with each other the samples collected in the framework of this study. But, it has to be sharing in two directions. And clear arrangements are made from the first day on who receives what and who will be mentioned on which position in publications.*[48]"

4 Discussion

4.1 Right of custodian to decide on access to HBM and data

The legal framework of many countries – including the countries that were the object of this study – stipulate that RECs need to provide an independent opinion on studies on human beings. More recently, REC were also given the competence to provide an opinion on research projects that use HBM and data stored in biobanks. A previous empirical study (see chapter 1) revealed that the majority of the biobanks establish their own committees to exercise a certain control on access to their collections of HBM and data (hereafter called "access committee"). The interviews investigated to which extent custodian – often represented by access committees – and RECs should evaluate access requests.

All informants agreed that custodians can evaluate the availability and suitability of HBM and data for particular research projects and the impact of the provision of HBM and data on the existing collection. They could prioritize particular types of research.

There was no consensus on whether custodians should evaluate the quality, the scientific and medical usefulness and the ethical value of research projects. Some informants suggested that the custodian would follow the advice of an ethics committee or funding body. They proposed that the custodian would consult external experts or would delegate such decision to subcommittees in relation to specific collections of HBM and data. Two informants suggested that the applicable criteria would be determined via binding legislation and that the custodian would only dispose of a limited discretionary power to apply such criteria. Custodians could also be required to demonstrate that their access committee disposes of sufficient relevant expertise, that it can evaluate access requests in an independent, non-discriminatory and objective manner. They could furthermore be expected to sufficiently motivate their decision and policy.

These different requirements imply that the custodian is not entirely free to decide how to allow access to his collection of HBM and data. The custodian would have to fulfil certain conditions in the evaluation of an access request; those conditions could be justified by the need to protect the rights and interests of the donor and/or the applicant.

---

[48] Translation by the authors of the following excerpt in Dutch: "*Ik zit nu in een groot consortium met farmaceutische firma's en zij stellen eigenlijk heel gemakkelijk hun stalen ter beschikking. Die verzameld zijn in het kader van die studie, men deelt dat met elkaar. Maar, het moet een delen aan de twee kanten zijn. En er worden vanaf dag één inderdaad (…) goede afspraken over gemaakt, over wie wat krijgt, over wie waar staat op de publicaties.*"

Quite some authors shared the opinion that access requests should be evaluated by independent committees that dispose of the necessary multidisciplinary expertise (11,23,105,106). This requirement was motivated by the desire to avoid potential conflicts(2), to protect the interests, safety and wellbeing of the donors and to ensure that HBM and data is used in a meaningful way (106). Article 19 of the Recommendation 2006(4) of the Council of Europe[49] contains the requirement to establish an independent oversight of population biobanks, as well as regular audits of the implementation of the procedures that apply to access to and use of HBM. Article 24 of the Recommendation 2006(4) stipulates the obligation to conduct an independent examination of the scientific merit of a research project, the importance of the aim of research and the verification of the ethical acceptability[50].

Authors stressed the importance of clearly defining the mandate of access committees and the criteria and procedures used to evaluate access request (11,16,105). One will notice in this respect that article 14 (c) of the Recommendation 2006(4) provides that one should specify the conditions governing access to and use of the HBM. Several authors are in favour of giving the access committee a rather broad mandate to evaluate access requests, including the scientific quality of the research project (81,96,106). One author argued that only a biobank – represented by the custodian – has the right to finally decide on access request (25). Other authors stressed the importance of clarifying and stimulating the interaction between ethics committees and access committees (105). One possibility would be that the activities of access committees would be supervised by ethics committees (23). One could refer in this respect to the fact that the future article 22 § 1 of the Belgian Act on HBM provides that the aims and the activities of a biobank have to be reviewed by an ethics committee.

The conditions imposed on the custodian with respect to the evaluation of access requests, raises the question whether an applicant could claim a fair or equal right to access and use (publicly funded) collections of HBM and data. If such right would exist, it would in any case not be absolute. The applicant can only use HBM and data for a certain period of time and for a research project that corresponds with the informed consent and the approval by the ethic committee. The project furthermore needs to comply with other legal requirements in relation to the conduct of biomedical research. The informants supported the idea that the custodian could require that applicants provide a short synopsis of the research project. There was no consensus on the extent to which applicants could be required to submit a more elaborate protocol with a description of the objective(s), design, methodology, statistical considerations and organization of a project. Such requirement is often applied in the framework of clinical studies on human beings and was suggested in a report of the National Cancer Research Institute, the National Cancer Intelligence Network and onCorde UK(96).

[49] Recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin

[50] The current text of the Recommendation 2006(4) only contains rules on ethics committees and does not relate to access committees.

4.2 Priority access right of collector/applicant

The right of the custodian to decide on access to HBM and data could be influenced by the fact that a clinician/researcher has taken the initiative to start a specific collection of HBM and data. Such clinician/researcher may expect to be informed and/or consulted in the decision to grant access to others to the collection of HBM and data(25). Such clinician/researcher could furthermore be granted a priority right – compared to other researchers – to use the HBM and data and to publish the results of his research(16,106). Finally access might be restricted to HBM and data collected in the framework of prospective studies, longitudinal population based studies or clinical trials.

There was a consensus that priority rights should only be granted for a limited period of time and that the custodian holds the final right to decide on access to the specific collection of HBM and data.

One should be aware that granting priority rights to particular collectors/applicants should not unnecessarily restrict access to collections of HBM and data. Article 101 TFEU[51] prohibits "*all agreement between undertakings, decision by associations or undertakings and concerted practices which may affect trade between Member States and which have as their object or effect the prevention, restriction or distortion of competition within the internal market*[52]." The prohibition of article 101 TFEU applies amongst others to agreements that *"(a) directly or indirectly fix purchase or selling prices or any other trading conditions; (…) (d) apply dissimilar conditions to equivalent transactions with other trading parties, thereby placing them at a competitive disadvantage; (…) (e) make the conclusion of contracts subject to acceptance by the other parties of supplementary obligations which, by their nature or according to commercial usage, have no connection with the subject of such contracts*." Article 101 § 3 TFEU contains a number of exceptions to the general prohibitions. The prohibition of article 101 § 1 does not apply to agreements, decisions and concerted practices, which "*contribute to improving the production or distribution of goods or to promoting technical or economic progress, while allowing consumers a fair share of the resulting benefit*, *and which does not: (a) impose on the undertakings concerned restrictions which are not indispensable to the attainment of these objectives; or (b) afford such undertakings the possibility of eliminating competition in respect of a substantial part of the products in question*." One should therefore be careful not to grant too extensive priority rights to particular researchers or research institutes that collect HBM and data for the biobank. Such priority right should not result in a situation where other researchers or research institutes no longer have the possibility to access the collection of HBM and data of a particular biobank and where such researchers or research institutes are placed at a competitive disadvantage. It this case, the priority right would in reality results in exclusive access to the collection. Article 101 TFEU has been applied to many different types of agreements – including material transfer agreements – that contain an element of exclusivity(107). Article 101 TFEU might also apply to agreements among (custodians of) banks of HBM or agreements, concerted practices or decisions of

[51] Treaty on the Functioning of the European Union

[52] The national competition legislations of the different Member States of the European Union provide similar prohibitions of agreements, decisions and concerted practices that have as object or effect to prevent, restrict or distort competition.

biobank organizations that would result in limitations on access to biobanks or exclusive access for particular applicants. Finally article 102 TFEU might apply when one could demonstrate that a biobank with a dominant position would abuse this position in refusing access or giving access under certain (unreasonable) conditions to applicants.

4.3 Right of custodian to decide on leftover HBM

Nearly all informants agreed that the applicant should, at least, inform the custodian when HBM is leftover at the end of the project. There was furthermore consensus that an applicant that wants to use leftover HBM in a new or follow-up project, has to submit a new request or an amendment to the initial request. The access committee or ethics committee will need to approve such new request or amendment. All informants agreed on the fact that the custodian could prohibit the applicant from transferring HBM (and data) to a third party. A. Boggio came to a similar conclusion in a previous study (108). Taken into account the above, we are of the opinion that the informants recognize the right of the custodian to decide – whether or not in collaboration with the ethics committee – upon the fate of leftover HBM.

There was no consensus on the criteria that should apply to determine whether the biobank should require the return or destruction of leftover HBM. This may not be surprising, since other studies revealed that different policies are applied by biobanks in this respect(17,67). Quite some informants referred to the fact that custodians and applicants agree on the return or destruction of leftover HBM at the time of approval of the access request. This would imply that the custodian would (have to) negotiate with the applicant at the time of the access request on a case-by-case basis on the return or destruction of leftover HBM. The “International Charter of principles for sharing bio-specimens and data” however suggests that ”*control of the bio-specimens remains with Provider, who can at any time demand the return or destruction of data and bio-specimens if a breach in the agreement occurs*.” (106) The final decision whether to return or destroy research results would thus remain with the custodian of the biobank.

Considering the fact that it does not seem possible to formulate general criteria to decide on the return or destruction of leftover HBM, it seems undesirable to regulate it via legislation. Biobanks could however clarify in their access arrangements, which criteria the biobank will take into account to decide on the return of destruction of leftover HBM, such as the type, quality, reusability and amount of leftover HBM. A general policy would limit the possibilities to negotiate on a case-by-case basis on the return or destruction of leftover HBM.

4.4 Right of biobank to participate in benefits

The interviews confirmed that the access fees charged by biobanks are often not enough to recover all costs in relation to the collection and storage of HBM and data. Some authors confirmed that it could be justified to charge higher access fees to external or industrial applicants that did not contribute (directly or indirectly) to the collection of HBM and data(16,25). One should, however, make sure that charging different access fees does not does not violate the principle of the free movement of goods (art. 30-36 TFEU). This could be the case if those different access fees would constitute an unjustified

hindrance to the import or export HBM and data between the different Member States of the European Union. Article 30 TFEU prohibits customs duties and charges having equivalent effect. Article 34 and 35 on TFEU prohibits quantitative restrictions on imports and exports of goods and all measures having equivalent effect. The prohibition to enact “measures having equivalent effect” implies that one should not enact measures or rules that discriminate domestic goods compared to foreign goods. It is furthermore prohibited to impose measures that would hinder the import or export of “goods” between Member States of the European Union, even though those measures would apply both to foreign and domestic goods. Article 36 contains exceptions to article 34 and 35 and does allow quantitative restrictions or measures having equivalent effect, if such restrictions or measures are justified on a number of grounds enlisted in article 36, such as **“**public morality, public policy or public security” or “the protection of health and life of humans, animals or plants.” Prohibitions or restrictions can only be justified under article 35, if they do not “constitute a means of arbitrary discrimination or a disguised restriction on trade between Member States.” The prohibitions or restrictions also have to proportionated compare to the targeted aim. M. Peeters (109) and S. Panis (110) have argued that the free movement of goods presumably also applies to HBM (16,25).

One should furthermore ensure that charging higher access fees to external or industrial applicants does not violate article 101 TFEU. Article 101, § 1, d) TFEU prohibits agreements, decisions or concerted practices that “*apply dissimilar conditions to equivalent transactions with other trading parties, thereby placing them at a competitive disadvantage*.”

Others suggested that some of the benefits of research projects using HBM and data could be fed back into the biobank infrastructure(23,111). There was no consensus as to under which conditions the applicant would be required to share benefits of research projects. All informants seemed to agree that only stakeholders that provide a scientific contribution would be entitled to participate in the benefits of a research project. This may be in line with the fact that most IPR legislations only grant IPRs to those individuals that provided an intellectual contribution(106). Furthermore, guidelines of the International Committee of Medical Journal Editors and the Committee on Publications Ethics only grant authorship to individuals that participated in “drafting the article or revising it critically for important intellectual content” and “the final approval of the version to be published” (ICMJE, 2009). The provision of HBM or data for a research project is not considered a sufficient ground to grant (co-)authorship. In some cases biobanks may provide important contributions to research projects via the collection, processing and organization of unique collections of HBM and data or the provision of scientific advice or assistance to the project. We would argue that the biobank should be recognized for such contribution(106,112,113).

Some authors promote in this respect the Bioresource Research Impact Factor (BRIF) initiative that aims to ”*promote the sharing of bioresources by creating a link between their initiators or implementers and the impact of the scientific research using them*.” (106,114) Some informants suggested that applicants that intend to commercialize the results of the research project would pay an additional fee or tax for the use of publicly funded collection of HBM and data. Such public contribution fee could avoid discussions about how important the delivery of the HBM and data was for

the final outcome of the project. The generated fees or taxes could be dedicated to the funding of public healthcare and research infrastructure, including biobanks. The HUGO Ethics Committee has recommended in its Statement on Benefit Sharing that "*profit-making entities dedicate a percentage (e.g., 1-3%) of their annual net profit to healthcare infrastructure and/or to humanitarian efforts*." J. Bovenberg argued in favour of a specific tax on tissue and cell products directly developed from HBM and data "*as an effective, if indirect, mechanism for letting a community share in the benefits resulting from the efforts of the taxpayer concerned and to make a licensee pay for the exclusive use of natural resources*"(111). The author suggested that such tax would only be due when a research project resulted in actual profit for the applicant.

4.5 Obligation of applicant to share research results

There was consensus among the informants that applicants could be requested to share the results of research projects using HBM and data from publicly funded biobanks. Some informants doubted whether the custodian should impose it as a condition to allow access to the collection, since this could discourage researchers to use the collection(108). Previous studies confirmed that an increasing number of biobanks(67) and funding bodies(115) require researchers to make their research results publicly available. Such requirement is motivated by the desire to maximize the use of results of publicly funded research(113,116). Some authors also invoke the principle of reciprocity: researchers could be expected to share their results with stakeholders that contributed to the collection of HBM and data, such as biobanks and donors(106,108). One of the first documents to introduce such requirement in the field of genomic research was the data release policy of the Human Genome project (HGP), known as the 'Bermuda Principles' (1996) (115). Afterwards, several other international documents promoted sharing research results with other researchers and the community at large(105,106), such as the Fort Lauderdale Agreement (2003)(117), the OECD Principles and Guidelines for Access to Research Data from Public Funding (2007) (86), the Toronto Statement on Pre-publication Data Sharing (2009), and the Global Alliance for Genomics and Health's White Paper (2013)(118). However, a number of conditions need to be fulfilled to make the sharing of research results useful and acceptable for the researcher that generates the results. Infrastructure needs to be available to store the research results in a proper way and to allow other researchers to access and use the results(116). Clear rules should be created to evaluate requests for access to such research results. Researchers may be hesitant to share their research results if they do not receive recognition for their investments in generating the results(106). Several authors pointed out that the legitimate interests of the researchers and the institutions and funders supporting the project should be respected. These interests may be the right to keep some research results confidential, to obtain IPRs in relation to research results and a priority right to publish research results(105,106,108,116,119).

Table 5 Pre-conditions to share research results

Infrastructure to store and share research results	Consensus
Rules on access to research results	Consensus
Recognition of researcher that generated results	Consensus
Respect interest of researcher that generated results	Consensus

5 Conclusion

The interviews with different stakeholders revealed a rather complex web of rights and obligations allocated to the custodian and the applicant in relation to access to HBM and data stored in biobanks and used for research projects (see Annex 5). The results did not allow creating a complete overview picture of the rights and obligations that the custodian and the applicant hold or should hold in relation to access to and use of HBM and data. Some rights and obligations are negotiated on a case-by-case basis, while others are stipulated in access arrangements. Furthermore, custodians and applicants can only exercise certain rights, when they fulfil particular obligations and conditions. There did seem to be a consensus on the attribution of certain general rights to the custodians and the applicant (see also Table 6). First, the informants agreed that the custodian of a biobank can, under certain conditions, evaluate access requests. There was however no consensus on how extensive the evaluation of an access request should be and to which extent the custodian of biobank should evaluate the scientific merits of an access request. Second, the informants agreed that industrial and external applicants could access biobanks under the same conditions as internal applicants. Different access fees might however be applied to industrial or external applicants. Third, there was a general consensus that one should not grant exclusive access to collections of HBM and data. One can, however, provide a preferential or priority right to collectors of HBM and data during a limited period of time. Fourth, most informants agreed that a custodian of a biobank could request the sharing and return of research results and that some of the benefits of research projects should be fed back into biobanks. There was, however, no consensus on how the custodian would exercise such rights in practice and which conditions the custodians would have to fulfil in this respect. Finally there seemed to be consensus that the custodian of the biobank has the final right to decide on whether leftover HBM should be destroyed or returned.

Table 6 Overview of main rights and obligations of custodians and applicants[53]

1. Rights and obligations in relation to decision on access to HBM and data	
A. Rights of custodian	Evaluate access request and decide on access to HBM
	Evaluate availability and suitability of HBM and data for project
	Evaluate impact on existing collection of HBM and data
	Determine priorities between different research projects
B. Obligations of custodian	Dispose of sufficient expertise/experience
	Act independently
C. Rights of applicant	Access collection of HBM and data
	Use HBM and data in research project
	Keep certain information confidential
	Priority access in case applicant collected HBM and data
D. Obligations of applicant	Use for specific project and certain time period
	Provide synopsis of project
2. Right to decide on leftover HBM	
A. Rights of custodian	Decide on return or destruction
	Decide on use in new or follow-up project
	Verify leftover HBM
	Provide minimum amount of HBM
B. Obligation of applicant	Inform biobank about leftover HBM
	Return or destroy leftover HBM
	Submit new request for new use of HBM
	Prohibition to transfer to third party
3. Right to participate in benefits of research project	
A. Rights of custodian	Charge access fee
	Request return of some of the benefits
	Share in benefits of research project
B. Right of applicant	Enjoy benefits of research project
C. Obligations of applicant	Pay access fee
	Return some of the benefits to biobank
4. Right to request the return of research results	
A. Rights of custodian	Request return and sharing of research results
B. Rights of applicant	Be informed and/or consulted on access to research results
	Receive sufficient recognition for returning research results
	Respect his legitimate interests

[53] We only included the rights and obligations on which most stakeholders agreed.

Part 3: Legal studies

Chapter 3: Legal framework governing access to biobanks

1 Introduction

The intention of the legal study on access to biobanks is to provide an overview of the legal framework applicable when (both academic and industrial) researchers want to access and use HBM and associated data stored in biobanks for research purposes. The study does not look into the conditions that apply to the use of HBM and data for diagnostic or therapeutic purposes. It should be noted however that some legislation affects all 3 of these different purposes.

2 Methodology

This legal study provides an overview and analysis of the most important legal instruments that apply to access to biobanks in Belgium and Denmark, at the international level and at the level of the Council of Europe.

We start the analysis from the legal framework in Belgium, since the PhD project was conducted within a Belgian research institute. We included legal instruments at the international level and at the level of the Council of Europe, since they might influence the Belgian legal framework. We chose to study the legal framework in Denmark, since it is considered as a pioneer in the development of biobanks networks, as well as in epidemiologic research. Denmark furthermore decided not to introduce specific legislation on biobanks[54].

The different legal instruments were analysed on the basis of the key access conditions defined in the previous empirical studies (Chapter 1 and 2) and supplemented with access conditions found in the different legal instruments. The 'key access conditions' were used to select the relevant legal instruments and describe and evaluate how the different legal instruments address 'access to biobanks'. We organized the evaluation of the legal instruments according to the following conditions: (a) the aims, activities and policies of biobanks; (b) custodianship; (c) the evaluation of access requests by access committees and research ethics committees; (d) intellectual property and commercialization; (e) benefit sharing; (f) sharing and returning of research results; and (g) the protection of personal data.

The legal study starts with a description of the legal framework applicable to access to biobanks[55] in Belgium (section 2), at the international level (section 3) and at the level of the Council of Europe (section 4). Section 5 contains a comparison of the Belgian legal framework with the international normative instruments and Recommendation (2006)4 and the Working Document of the Council of Europe. Section 6 describes the legal framework applicable to access to biobanks in Denmark and compares it with the legal framework applicable in Belgium. In the conclusion we summarize to which extent the rights and obligations of the custodian and the applicant are regulated via the existing legal framework.

[54] The methodology section (2.2) of the General Introduction contains a more detailed explanation why we have chosen Denmark.
[55] We do not aim to provide a complete description of the applicable legal framework, but rather focused on access to biobanks.

3 Belgian legal framework applicable to access to biobanks

3.1 Act of 19 December 2008 on the procurement and use of human bodily material

3.1.1 Introduction

The Belgian Act of 19 December 2008 on the procurement and use of human bodily material (hereafter the Act on HBM) has been enacted to implement the EU Directives 2004/23/EC[56], 2006/17/EC and 2006/86/EC. The latter itself implemented EU Directive 2004/23/EC. The Act on HBM entered into force on 1 December 2009, with the exception for the provision on biobanks.

Directive 2004/23/EC only relates to human tissues and cells intended for application on humans. The Act on HBM on the other hand, also intends to regulate the use of HBM and data for research purposes.

The initial text of the Act on HBM contained legal rules on the procurement and use of HBM by biobanks for research purposes. These initial rules never entered into force and have been replaced by an Act of 19 March 2013 containing diverse provisions in relation to health. An Act of 14 April 2014 containing diverse provisions in relation to health introduced a specific legal framework for biobanks created in the framework of a clinical study. The legal framework for (research) biobanks – stipulated in both acts – will only enter into force after the publication of one or more executive Royal Decrees in relation to biobanks (art. 124 of the Act of 19 March 2013 and art. 139 of the Act of 14 April 2014). It is uncertain when such Royal Decrees will be published.

3.1.2 Scope

The Act on HBM provides a legal framework for the procurement and use of HBM for medical applications on humans or for research purposes (art. 3 § 1). It does not apply to the removal of organs for transplantation (art. 3, § 3, a) or autologous applications within the same surgical procedure (art. 3, § 3, c). Nor does it apply to the removal and other operations conducted on HBM for pure diagnostic purposes – in favour of the donor – and to the extent that such HBM is not intended for any other purpose (art. 3, § 3, d)(35).

The Act on HBM applies to every operation relating to the donation, removal, procurement, testing, processing, preservation, storage or distribution of HBM. The distribution includes the import and export of HBM (art. 3 § 1).

The Act on HBM in principle applies to all human biological/bodily material (hereafter 'HBM'). It particularly applies to human tissues and cells and all derived substances irrespective their degree of transformation (including stem cells) (art. 2, 1° and 3 §2). The Belgian Act on HBM is thus in principle also applicable to DNA and proteins (120). The Act on HBM also applies, to a limited extend, to gametes, embryos and foetuses (art. 3 § 4). It equally bears upon the removal, donation, procurement and testing of HBM for advanced-therapy medicinal product (ATMP), but not to other operations in this

[56] EU Directive 2004/23/EC of the European Parliament and the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

respect (art. 7 § 4). Legislation on medicinal products applies in this respect. The Act on HBM only applies to regenerative HBM, such as blood, blood substances, (body) hair, nails, urine, mother milk, faeces, tears and sweat, when such HBM is procured, stored or provided for scientific research (future art. 3 § 3).

The Act on HBM applies when the removal of HBM occurs on the Belgian territory(110,120).

3.1.3 Different organisations

The Act on HBM established four types of organizations in relation to the procurement and use of HBM. These four types of organizations are banks for HBM, intermediate structures, production establishments and biobanks (art. 2, §1, 24°-27°). The distinction between the four types of organizations is quite unique and does not exist in other countries. The first three types of organizations – banks for HBM, intermediate structures and production establishments – are established to conduct operations on HBM to the extent that they relate to diagnostic or therapeutic applications on humans. The fourth type of organization – a biobank – was established to conduct operations that pertain to the use of HBM for research purposes.

A bank for HBM can conduct all operations in relation HBM. It has the exclusive competence to procure HBM – for applications on humans – and to decide on the allocation of HBM to a particular patient in the framework of a therapeutic application (art. 2, §1, 24°).

An intermediate structure for HBM has a more limited competence, since it cannot procure, test or decide on the allocation of HBM. The custodian of a bank for HBM will have to authorize the procurement and allocation of HBM by an intermediate structure (120). An intermediate structure can procure HBM for the production of advanced-therapy medicinal products (ATMP), if it concludes a collaboration agreement with a bank for HBM (art.8, §2).

A production establishment can only conduct operations in relation to the industrial production of autologous medicine[57]. Furthermore it cannot decide on the allocation of HBM[58].

A biobank can conduct all operations in relation to the procurement, storage and provision of HBM and possibly also associated data exclusively for research purposes. It cannot conduct any operations or research relating to (medical) applications of HBM on humans (art. 2, §1, 27°). Since the specific legal provisions on biobanks have not entered into force yet, no hospital or company formally established a biobank up to this day.

[57] These are products relating to somatic cell therapy, gene therapy or tissue engineering intended for therapeutic and prior determined mere autologous use.
[58] A production establishment was initially not entitled to test HBM, but was given the right to conduct such testing in the Act of 19 March 2013.

3.1.4 Aims and activities

In the future an ethics committee will need to provide a positive advice on the aims and activities of a biobank. As opposed to the other type of organizations, the biobank does not have to obtain an accreditation from the Medicine Agency. It only has to notify the Medicine Agency of its establishment and activities (future art. 22, § 1, first section). An Act of 14 April 2014 introduced an exception on this rule. The exception applies to biobanks that are created in the framework of a clinical trial – as regulated by the Act of 7 May 2004 on experiments on humans. In this case, the approval of the clinical trial by the Medicine Agency would replace the requirement to notify the establishment and activities of a biobank to the Medicine Agency (future art. 22, § 1, section 2). Furthermore, the positive advice of the ethics committee on the clinical trial will also be considered as a positive advice on the activities and aims of the biobank (future art. 22, § 1, section 6). However biobanks created in the framework of a clinical trial can only procure, process, store and make HBM available for the aims and the design of the clinical study as defined in the protocol.

3.1.5 Rights and obligations of the custodian[59]

According to the Act on HBM, the custodian has many different rights and obligations in relation to HBM. Some of those obligations can only be exercised by the custodian of a bank for HBM. In the future a custodian of a biobank will have similar obligations in relation to HBM used for research purposes. Other obligations can be exercised by custodians of the four different types of organizations. We will focus on the obligations of a custodian of a biobank.

In the future the custodian of a biobank will have the obligation and right to decide on the allocation of HBM for research purposes (art. 2, 27°). The custodian will also be responsible for the return of information on traceable HBM to the donor (art. 11). The custodian will have to ensure that the informed consent of the donor is respected (art. 15 and art. 22 § 3). Furthermore, the custodian will have to make sure that the ethics committee provides a positive advice on the secondary use of HBM (art. 21, last section). The custodian of the biobank will act as contact person towards the Medicine Agency(121) and the ethics committee. She/he will have to verify the quality of the HBM and the safety and quality of operations conducted with the HBM (art. 16). The custodian will need to conclude the necessary insurances (art. 17 § 4).

Finally, the custodian of the biobank will be responsible for the processing of personal health data. In case the biobank procures traceable HBM, the custodian needs to be a physician. In case the biobank procures non-traceable HBM, the custodian has to be a physician or a pharmacist (art. 22, § 3).

[59] The Act on HBM uses the terms ‘beheerder’ in Dutch and ‘gestionnaire’ in French’

3.1.6 The removal of HBM

The Act on HBM regulates the removal of HBM for medical applications as well as for scientific research. The removal of HBM is only permitted on the condition that it corresponds to a specific finality or purpose (art. 8, § 1, section 1, 1°). When HBM is removed for scientific research, the aim of the removal should be precise and relevant for this scientific research. The finality should be specified (art. 8, § 1, section 1, 1° and 2°). Specific rules are applicable to the removal of HBM from minors or persons incapable to consent (art. 10 § 3).

HBM can only be removed from the donor with his prior consent (art. 10 § 1). Such consent should be informed, conscious and free. The consent should be given in writing and should be dated and signed (art. 10 § 5). Consent is not required in case HBM is removed for a direct preventive, diagnostic or therapeutic purpose in favour of the donor (art. 9). The donor has the right to withdraw his consent at any moment and does not have to motivate such withdrawal (art 10 § 5, section 4). When HBM is removed from a deceased donor, the Act on HBM creates a presumption that the donor consented to such removal unless he or she explicitly objected to it before (art. 12).

3.1.7 The use of HBM

Article 2, 19° of the Act on HBM defines the use of HBM as any application of HBM that follows the last operation conducted with the HBM (such as the distribution of HBM). The Act on HBM regulates the use of HBM pertaining to medical applications on humans or in scientific research. The use of HBM for medical applications requires a preventive, diagnostic or therapeutic purpose that is based on a precise scientific foundation. The use of HBM in scientific research requires that the purpose is relevant for such research and has a precise finality (art. 8 § 1, 2°).

The Belgian legislation distinguishes between primary use and secondary use of HBM (art. 10 § 1 and 20). Primary use of HBM is defined as every use of HBM to which the donor explicitly consented in the framework of the removal of the HBM (art. 2, 29°). Primary use requires the consent of the donor – prior to the removal of HBM. This consent should be informed, conscious and free (art. 10 § 1 and § 5). The consent should be in writing, dated and signed by the donor. The donor in principle has the right to withdraw his consent at any moment. The donor should however express such withdrawal before the moment that the HBM undergoes any operation after the procurement (art. 10 § 1 & 5 section 4). We agree with other authors that the right of withdrawal becomes rather symbolic, since the donor loses such right as soon as the custodian stores or processes the HBM (120).

Secondary use of HBM is defined as any other use of HBM than the use to which the donor explicitly consented in the framework of the removal (art. 2, 30°). Secondary use of HBM also requires a prior consent of the donor that should be informed, conscious and free (art. 20 § 1). The consent should be in writing and dated and signed by the donor (art. 10 § 5). The requirement to obtain informed consent for the secondary use of HBM does not apply in 2 exceptional situations: (i) when requesting such consent is impossible – for example when the donor passed away – (art. 20, § 1, second section); (ii) when requesting such consent is exceptionally inappropriate – for example because of the critical health status of the donor –; (art. 20, § 1, second section).

An ethics committee of a university hospital or another competent ethics committee[60] has to provide a positive advice on both the secondary use of the HBM and the specific aims of such use (art. 21). It evaluates the relevance of the secondary use and the design. It also evaluates the adequacy of the information provided to the donor, the scope of the informed consent (if required) and whether it is sufficiently specific (art. 21, section 3, 1° and 2°). Finally it will evaluate whether it appears impossible or exceptionally inappropriate to request consent from the donor (art. 21, section 3, 3°). The future art. 22, § 1, section 7 and 8 stipulates an exception to the required positive advice of an ethics committee for the secondary use of HBM for research purposes. This advice will not be required, if the proposed use of HBM falls within the scope of the aims and activities of the biobank and the ethics committee provided a positive advice on those aims and activities.

Finally the Act on HBM created a presumption that the donor consents to the use of residual HBM[61] for scientific research, when he does not object to such use prior to the conduct of any operation on the HBM. The donor or his representative has to be informed in advance about the use of his residual HBM. He must be informed of the possibility to object to such use (art. 20, § 2). An ethics committee will have to provide a positive advice on the use of residual HBM for research purposes (art. 21).

3.1.8 Traceability

When HBM is used in the framework of scientific research in biobanks, the donor or his representative regarding the removal of HBM can decide whether the HBM should remain traceable.[62] In case the donor passed away or in case of residual HBM, the provider of the HBM to the biobank can decide on the traceability (future art. 22, § 4). Such provider could be, more particularly, the custodian of a bank for HBM, an intermediary structure or a production establishment, a physician in the concerned laboratory or the chief physician in the concerned hospital. The custodian of a biobank shares the obligation to guarantee the traceability with all persons that use HBM originating from a biobank. They should make sure that all necessary measures are taken and all necessary information is provided to guarantee the traceability of HBM, unless it has been decided to abandon such traceability (future art. 22, § 5). It seems advisable that biobank policies or the agreements with their users would contain clear arrangements on how to share this obligation.

[60] Such committee has to comply with the conditions set out in art. 2, 4° (and art. 11 *ter) of the Act of 7 May 2004 relating to experiments on human beings.*

[61] Residual HBM is defined as the part of HBM that was removed for diagnostic purposes or treatment of the donor and that – after a sufficient and relevant part has been stored to conduct, refine or complete the diagnosis or treatment of the donor on the basis of new scientific data – has become redundant for such purposes and therefore could be destroyed (art.2, 33°).

[62] The traceability is the capacity to localize and identify the HBM during all step of the process, in particular the procurement, processing, preservation, storage and distribution of HBM in order to be used or destroyed.

3.1.9 No (commercial) advantage

Article 6 prohibits offering or receiving any financial or material advantage in exchange for the donation of HBM. The donor can receive a reimbursement of costs or loss of income incurred as a direct consequence of the donation. The banks for HBM – or the biobank in the future – and the persons responsible for the removal of HBM can receive a reimbursement of costs caused by the removal and operations conducted in the concerned bank for HBM. Condition here is that the removal and operations are not conducted with the aim of generating profit. Article 8, § 1, 9° prohibits the payment or receipt of a material compensation for the transfer, procurement or receipt of HBM that has not been subject to any transformation/processing – in a bank for HBM, an intermediate structure or a biobank – to make the HBM suitable for an application on humans or scientific research. HBM as such cannot result in the payment of any material compensation. One can however request a financial compensation for the operations of the transformation/processing and manipulation of HBM.

3.1.10 Distribution of HBM by the biobank

Prior to the distribution of HBM, the custodian of biobank will have to conclude an agreement with the person or institute(s) to whom HBM is distributed. This agreement needs to contain amongst others rules on the possible processing of personal data by the person of institutes to whom the HBM is distributed (future art. 22, §2, section 3 and 4). The modalities of such an agreement have not been defined (yet)

3.1.11 Transfer of HBM across national borders

The import of HBM into Belgium from a country outside the EU or the export of HBM to a country outside the European Union is – in principle – only allowed when such import or export is conducted under the supervision of an organization – such as a bank for HBM or a biobank – established in the European Union (3).

The import of HBM from another country (inside our outside the EU) into Belgium or the export of HBM towards another country (inside or outside the EU) is only allowed, when the custodian of the bank for HBM demonstrates that the HBM complies with the – quality – requirements stipulated in the Act on HBM and the Royal Decrees in execution of the Act on HBM[63](110).

When HBM imported in Belgium is finally destined for exportation to another country (inside or outside the EU), the HBM only has to comply with the quality requirements imposed in the final country of destination. This is due to the fact that the HBM will only be stored in Belgium for a limited period of time and the HBM will not be used in Belgium.

A bank for HBM – and in the future a biobank – has in principle the exclusive competence to import HBM into Belgium. HBM can only be exported outside Belgium under the supervision of a bank for HBM – or in the future a biobank – or an intermediate structure that obtained authorization from the custodian of a bank of HBM for such export (art. 8, § 1, 7° of the Act on HBM) (110,121).

[63] Art. 18 of the Royal Decree of 28 September 2009 containing quality and safety norms for the donation, removal, procurement, testing, processing, storage and distribution of HBM.

3.1.12 Future Royal Decrees in relation to biobanks

The specific provisions in relation to biobanks will only enter into force upon the publication of one or more executive Royal Decree in relation to biobanks (art. 124 of the Act of 19 March 2013 and art. 139 of the Act of 14 April 2014). Such royal decrees may contain more detailed provisions on (a) the notification procedure to the Medicine Agency; (b) the positive advice of an ethics committee in relation to the activities and aims of the biobank; (c) the registry that a biobank should maintain in relation to its activities; (d) the traceability and identification of donors; (e) the specific conditions applicable to the removal of HBM for research purposes. An initial proposal of Royal Decree had been circulated to different stakeholders. It is uncertain whether this proposal and/or the specific provisions on biobanks will ever enter into force. A new government has taken office in October 2014. The new Minister of Health announced in her policy note that the legal framework applicable to biobanks would further be modified and approved.

3.2 Privacy and data protection legislation

3.2.1 Introduction

Most biomedical research does not only require access to HBM. It also requires access to associated data about the characteristics of the HBM and the health status and other data related to the donor, such as demographic data and data on previous diseases and treatments. Researchers need access to this data to be able to choose the right type of HBM for their research project and to interpret the research results in a correct manner.

At the level of the European Union Article 29 Data Protection Working Party[64] considered "the extraction of information from human tissue samples a collection of personal data, to which the rules of the Data Protection Directive apply"[65].

In its Opinion n° 10/2009[66], the Belgian Privacy Commission pointed out that the Act on HBM and the executive Royal Decrees stipulate that every time an operation is conducted on HBM, information has to be provided about a number of biological and medical characteristics of the donor. The Privacy Commission concluded that (data about) those biological and medical characteristics of the donor should be considered personal data. This is in relation to the health of the donor in the sense of art. 7 of the Privacy Act[67] to the extent that the identity of the donor becomes available or accessible (121).

Both opinions confirm the importance of the protection of personal data for biobanks. That is why we decided to discuss the most important provisions of the Belgian Privacy Act that apply when HBM and data are processed in the framework of scientific research.

---

[64] The Article 29 Working Party is an advisory working party at the level of the EU made up of a representative from the data protection authority of each EU Member State, the European Data Protection Supervisor and the European Commission.
[65] Opinion n° 4/2007 of on the concept of personal data of the Article 29 Data Protection Working Party, p. 9
[66] Opinion n° 10/2009 of the Belgian Privacy Commission on the 4 Royal Decrees executing the Act on HBM.
[67] The Privacy Act is the Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data

3.2.2 Definitions

Article 1 of the Privacy Act defines a number of key concepts. Personal data is defined as "*any information relating to an identified or identifiable natural person*, while an identifiable person *is defined as "a person who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural, or social identity*" (art. 1, § 1 Belgian Privacy Act).

Processing of personal data is defined as "*any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as the collection, recording, organization, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction of personal data"*; (art. 1, § 2 Belgian Privacy Act)

The controller is the "*person or organization that determines, alone or in collaboration with others, the purposes and means of the processing of personal data*." The custodian of the biobank would be considered as controller, when personal data is processed in the framework of a biobank. The processor is "*the person or organization that processes personal data on behalf of the controller*" (art. 1, § 4 Belgian Privacy Act).

3.2.3 General principles

Article 4 of the Privacy Act contains a number of general principles that apply to the processing of all kind of personal data. First, the personal data has to be processed in a fair and lawful manner. Second, the personal data has to be collected and processed for specific, explicitly defined and legitimate purposes and the controller (and/or processor) has to make sure that the personal data is accurate, adequate, relevant and not excessive. Finally the personal data should be stored in a secure and confidential manner and no longer than necessary.

3.2.4 Rights of the data subject[68]

Personal data have to be processed in accordance with the data subject's rights. These rights more particularly cover the right to information, the right to consent and the right to access the personal data.

Each fully or partially automated processing of personal data should also be notified to the Privacy Commission. Such notification should occur prior to the processing of personal data. For each separate purpose a new notification has to be conducted, unless different purposes are connected (art. 17).

[68] When personal data is processed in the framework of the biobank, the data subject will be the donor of HBM and data to the biobank.

3.2.5 The processing of health data in the framework of scientific research

The processing of health data is in principle prohibited on the basis of article 7, § 1 of the Privacy Act, since such data is considered particularly sensitive personal information.

Article 7, § 2, k does allow the processing of health data if such processing is necessary for scientific research and if the processing is conducted in compliance with the Royal Decree of 13 February 2001. This exception makes it possible under certain conditions to collect and process health data in the framework of biomedical research, clinical trials or biobanks.

The Privacy Act provides different rules depending on whether the personal health data is initially or subsequently processed in the framework of scientific research.

The initial processing of data for scientific research can occur when the participant provided an informed consent to participate in the research project or clinical trial. It may be advisable, but it is not a legal requirement to obtain a separate consent of the participant to process its personal data for this purposes.

Another possibility is that personal health data was initially processed in the framework of health care and only subsequently processed and used for scientific research. This situation is regulated by a Royal Decree of 13 February 2001, which in principle only allows the processing of anonymised health data (art. 3 Royal Decree).

Subsequent processing of coded data is exceptionally allowed, when one demonstrates that it is impossible to use anonymised data. In this case the notification to the Privacy Commission has to contain an explanation why anonymised data could not be used (art. 4 Royal Decree). Prior to the coding of the data, the data controller and/or data processor furthermore has to communicate the following information to the data subject: (1) the identity of data controller; (2) the categories of processed personal (health) data; (3) a detailed description of scientific purpose of processing; (4) the recipients or categories of recipients of personal data; (5) the existence of right to access and rectify his/her personal data and to oppose processing of personal data (art. 14 Royal Decree). In case it would appear impossible to provide such information to the data subject, the data controllers has to explain to the Privacy Commission why this is impossible. The Privacy Commission can provide a recommendation in this respect and can require additional conditions for processing coded information under these conditions (art. 16 Royal Decree).

Subsequent processing of non-coded or identifiable personal data is only possible, when one demonstrates that it is impossible to use anonymised or coded data (art. 5 Royal Decree). In this case, the notification to the Privacy Commission has to explain why anonymised or coded data could not be used and the data controller or processor has to communicate the information mentioned above to the data subject. Finally the data controller or processor has to obtain the prior and explicit consent of the data subject for subsequent processing of non-coded personal data for scientific research. A prior and explicit consent of the data subject does not have to be sought in case the data is manifestly made public by the data subject or if it is impossible or unreasonably burdensome to obtain a prior and explicit consent (art. 18-21 Royal Decree).

3.2.6 Access to health data by the data subject (or donor)

The data subject in principle has the right to access health data processed in the framework of scientific research (art. 10 § 2, section 1 Privacy Act). At the request of the data subject or the data controller such access to health data can occur with the assistance of a healthcare professional. Exceptionally the controller can postpone access to health data processed in the framework of medical scientific research – for example in the framework of a double blinded tests, if (i) there is no risk of an infringement on the privacy of data subject; (ii) such access would be detrimental to medical scientific research; and (iii) if data subject explicitly consented to the postponement (art. 10 § 2, section 2 Privacy Act).

3.2.7 Transfer of health data to a third party

The transfer of health data by the data controller to a third party – such as an applicant – is subject to several conditions. First, the data controller has to demonstrate that the transfer of health data is justified on legitimate grounds. This would for example be the case if the transfer occurs on the basis of written permission of the data subject or is necessary for purposes of a medical diagnose or scientific research.

In case health data is subsequently transferred for scientific purposes, the data subject has to be informed of the transfer of coded data or has to provide informed consent for the transfer of non-coded/identifiable data. Second, health data can in principle only be transferred to health professionals. Third, one should provide sufficient security measures in case of the electronic transfer of health data (for example E-Health Services). An important extra condition is the fact that one should in principle obtain a prior authorization by the Health section of the Sectorial Committee on Social Security and Health (art. 42, § 2, 3°, of the Act of 13 December 2006 containing miscellaneous provisions in relation to health) for each transfer of health data. This includes the transfer of health data in the framework of an experiment or clinical trial. Such prior authorization is not required, when the transfer occurs between health care professionals that are bound by a professional obligation of secrecy and are personally involved in diagnostic, preventive of health care acts relating to the patient.

3.2.8 The transfer of personal data across national borders

The EU Directive 95/46/EC[69] attempted to create a harmonized framework for the protection of individuals with regarding to the processing of personal data[70]. Under this harmonized framework personal data can be transferred between EU Member States. Article 1, paragraph 2 of the EU Directive 96/46/EC provides in this respect that EU Member States "*shall neither restrict nor prohibit*

[69] Directive 95/46/EC of the European Parliament and of the Council of 25 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

[70] On 25 January 2012, the European Commission published a Proposal for a Regulation on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation). The Proposal for a Regulation has been the object of a very strong debate between the European Parliament, the European Commission and the Council. No consensus has been reached yet on a final text. A General Data Protection Regulation would create one uniform privacy regulation that is directly applicable in the whole EU.

the free flow of personal data between Member States for reasons connected with the protection afforded under the Directive."

The transfer of personal data to countries outside the European Union is only allowed, when such countries offer an adequate level of protection and if the provisions of the Belgian Privacy Act are respected (art. 21 of the Belgian Privacy Act)(122). The European Union has concluded agreements with, amongst others, Andorra, Argentina, Canada, Switzerland and Israel confirming that they offer an adequate level of protection. The transfer of personal data to the US is only allowed, when the recipient of the personal data in the US is certified under the 'Safe Harbor' framework. The transfer of personal data to other countries can be authorized via Royal Decree and after the advice of the Privacy Commission, when the data controller provides sufficient guarantees for the protection of the personal data (art. 22 of the Belgian Privacy Act)(123).

4 International normative instruments applicable to access to biobanks

This section reviews a number of international normative instruments that are relevant for access to biobanks. The documents were selected after a review of the BBMRI report "Biobanks and the public: Governing biomedical research resources in Europe"(124) and an overview article of A. Cambon-Thomson et. al. describing trends in the ethical and legal framework for the use of human biobanks(23):

1. The Universal Declaration of Human Rights, proclaimed by the United Nations General Assembly in Paris on 10 December 1948.
2. The World Medical Association Declaration of Helsinki[71] entitled "Ethical Principles for Medical Research Involving Human Subjects[72]" (hereafter the "Helsinki Declaration"). The Helsinki Declaration contains ethical principles for medical research involving human subjects, including research on identifiable human material and data (§ 1).
3. The UNESCO Universal Declaration of 1997 on the Human Genome and Human Rights (hereafter UNESCO declaration)
4. The OECD Guidelines for Human Biobanks and Genetic Research Databases (2009) (hereafter "OECD Guidelines")
5. Recommendation of the European Society of Human Genetics, entitled "Data Storage and DNA Banking for Biomedical Research: Technical, Ethical and Social Issues" (2001) (hereafter ESHG Recommendation).

These international normative instruments do not have a binding legal force (except for the Universal Declaration of Human Rights), but they do have an important moral value.

The description and evaluation of the international normative instruments was conducted taken into account the "key access conditions."

[71] The declaration has been adopted by the 18th WMA General Assembly in Helsinki (Finland) in June 1964 and has been amended at several occasions. The last amendments have been adopted by the 64th WMA General Assembly in Fortaleza (Brazil) in October 2013

[72] The declaration has been updated on several occasions and the most recent version dates from 2013: www.wma.net/e/policy/b3.htm

4.1.1 Aims, activities and policies of biobanks

Several international normative instruments suggest that an independent Research Ethics Committee (REC) should review the establishment, governance, management, operation, access to, and use of biobanks and its protocols and processes for research activities (best practice 1.2 OECD Guidelines; see also § 19 ESHG Recommendation).

4.1.2 Custodianship

Custodians of biobanks should develop and maintain clearly documented operating procedures and policies for the procurement, collection, labelling, registration, processing, storage, tracking, retrieval, transfer, use and destruction of HBM, data and/or information (principle 1.F OECD Guidelines).

4.1.3 Evaluation of requests for access to HBM and data for research purposes

The international normative instruments contain an important number of rights and obligations in relation to how access requests should be evaluated.

The custodian should make the access policy and procedures publicly available (best practice 7.1 OECD Guidelines). He should create mechanism to review applications for access to HBM and/or data and the envisaged use of the HBM and/or data for consistency with the types of research uses agreed to by a participant (best practice 7.2-3 OECD Guidelines).

Access to HBM and data should be based on objective and clearly articulated criteria. It should be consistent with the research subjects' informed consent (principle 7.A. OECD Guidelines; see also § 21 ESHG Recommendation). The custodian of HBM should formulate criteria for prioritizing applications for access to HBM and data (principle 7.E. OECD Guidelines).

The custodian of a biobank has to ensure that any stratified access conditions and fees are fair, transparent and do not inhibit research (best practice 7.4 OECD Guidelines). The conditions of access of researchers to HBM and data should be set out in a material transfer agreement or another appropriate agreement (best practice 7.6 OECD Guidelines).

The researcher should draft a research protocol that describes and justifies the design and performance of the research study. The protocol should furthermore contain information about the funding and/or sponsors of the project, the institutional affiliations of the researcher, potential conflicts of interest, incentives provided to research subjects and information relating to the treatment and compensation of research subject who suffered harm due to the participation in the research study (§22 Helsinki Declaration; see also principle 7.B OECD Guidelines).

Each research protocol and amendments to such protocol have to be submitted for approval to a REC. (§23 Helsinki Declaration; see also art. 5 d) and 16 UNESCO Declaration). Such REC must act in a transparent and independent way and must be duly qualified. The REC can monitor on-going research project (§23 Helsinki Declaration; see also best practice 3.3 OECD Guidelines).

4.1.4 Intellectual property and commercialization

Custodians of biobanks should develop a clearly articulated policy on (i) the commercialization of HBM, associated data and research results and (ii) intellectual property rights (principle 9.D-E OECD Guidelines).

It is generally accepted that the donation, collection and provision of HBM and associated data, as such, should not give rise to any financial gain (125,126). Article 4 of the UNESCO Declaration stipulates in this respect “the human genome in its natural state shall not give rise to financial gains.”

4.1.5 Sharing in the advancement of scientific research and its benefits

Article 27 § 1 of the Universal Declaration of Human Rights states that “everyone has the right (…) to share in scientific advancement and its benefits” (see also art. 12 (a) of the UNESCO declaration and principle 9.B OECD Guidelines).

The best practice 9.1 of the OECD Guidelines stipulates that the custodians of a biobank should develop a clearly articulated policy on benefit sharing.

4.1.6 Sharing and returning of research results

Several international documents promote the sharing of research results with others researcher and the community at large, such as the ‘Bermuda Principles’ (1996)(115), the Fort Lauderdale Agreement (2003)(117), the Toronto Statement on Pre-publication Data Sharing (2009), and the Global Alliance for Genomics and Health’s White Paper (2013)(118).

The Helsinki Declaration and the OECD Guidelines equally address the sharing and returning of research results. Both international normative documents provide that researchers – together with sponsors, editors, publishers and custodians of biobanks – have an ethical obligation to publish and disseminate the results of research studies. Researchers should publish or make available in other ways both positive, negative and inclusive research results. (§35 Helsinki Declaration; see also principle 1.H of the OECD guidelines).

The OECD Guidelines furthermore suggest that custodians of biobanks should have a clearly articulated policy on whether and how the results of research and analyses carried out using HBM and data stored in biobanks should be returned to the biobank and be incorporated into its databases. They should also clearly articulate how access to such results for further research will be managed (principle 5.C OECD Guidelines).

4.1.7 Protection of personal data

Every precaution has to be taken to protect the privacy of the research subjects and the confidentiality of their personal information (§24 Helsinki Declaration; see also principle 1.D OECD Guidelines).

4.1.8 Consent

The international normative instruments contain several principles in relation to the requirement to obtain the informed consent of the donor for the use of his HBM and data for research purposes.

Paragraph 32 of the Helsinki Declaration formulates the general principle that one should seek informed consent for its collection, storage and reuse, when identifiable HBM or data is used in a research project. In case seeking such consent would be impossible or impracticable, the study may be done only after consideration and approval of a REC (see also best practice 3.1 OECD Guidelines and § 12 ESHG Recommendation).

The custodian of a biobank should inform donors of their right to withdraw. Donors should be informed of the nature, modalities, implications and limits to exercise that right. The donors in principles do not have to explain their withdrawal. The withdrawal should not have any negative consequences for the donors or their family in regards to the provision of healthcare services (principle 4.G. and best practice 4.13 OECD Guidelines; see also § 7 of ESHG Recommendation).

4.1.9 Balancing the rights and interests of the donor with the freedom of research

Paragraph 8 of the Helsinki Declaration provides that 'medical research cannot take precedence over the rights and interests of the research subject/donor' (see also art. 10 UNESCO Declaration and principle 3.C OECD Guidelines). This is an important principle, since it draws the attention to the fact that the rights of donors should be respected at any time. The principle is however not absolute and has to be weighed against other principles, such as the 'freedom of research'. Article 12 (b) of the UNESCO Declaration stipulates that the freedom of research "*is necessary for the progress of knowledge"* and even declares that such freedom *"is part of freedom of thought*."

The legal framework applicable to biobanks should aim to balance both principles. On the one hand, the interests of the donors should be protected in an optimal manner. On the other hand, one should not unnecessary hinder the possibility to use HBM and data in research projects. The optimal balance between both principles cannot be determined in a general way. Such balance can only be determined in each specific situation. One could refer in this respect to the fact that several international normative instruments – such as paragraph 32 of the Helsinki Declaration – require an informed consent of the donor for the use of his HBM and data for research purposes. However, the REC can authorize researchers to use the HBM and data without an informed consent, when it would be impracticable to obtain such consent.

5 Recommendation 2006 (4) of the Council of Europe

5.1 Introduction

A number of legal documents have been created in the framework of the Council of Europe in relation to biomedicine and biomedical research. We will not discuss the Convention on Human Rights and Biomedicine[73], since it applies to biomedical medicine and not to biomedical research on HBM. We will also not go into the Additional Protocol concerning Biomedical Research[74] that applies to biomedical research involving interventions on human beings.

We will instead focus on the Recommendation 2006(4)[75], since it specifically applies to use of HBM and data in biomedical research. Recommendation (2006)4 is not a legal binding document. The Recommendation, nevertheless, has an important moral value and could influence Belgian legislation in an indirect manner.

We will first discuss the most important provisions in relation to access to biobanks in the original text of Recommendation (2006)4. Afterwards we will have a look at the most important modifications suggested in the Working document on research on biological materials of human origin (hereafter the "Working Document'"). The Committee on Bioethics[76] published the Working Document on 18 March 2014 and elicited comments from the public by 15 August 2014. The revised text of Recommendation 2006(4) should be published in the beginning of 2015. We decided to discuss the most important modifications suggested in the Working Document, since they are particularly relevant for access to HBM and data stored in biobanks.

5.2 Overview of Recommendation 2006(4)

5.2.1 Protection of donors

Article 1 of Recommendation 2006(4) stipulates that member states *should protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity, right to private life and other rights and fundamental freedoms with regard to any research governed by this recommendation*.

Article 5 stipulates that the risk related to the research activities, in particular the risk to the private life, should (a) be minimized for the persons concerned and possible also their family; (b) not be disproportionate to the potential benefit of the research activities.

5.2.2 Prohibition of financial gain

Article 7 contains the important provision that HBM, as such, should not give rise to financial gain.

[73] The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (1997)
[74] Additional protocol to the Convention on Human Rights and Biomedicine, concerning biomedical research (2005)
[75] The Recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin
[76] The Committee on Bioethics is an intergovernmental body within the Council of Europe

5.2.3 Use of anonymised or identifiable HBM

Article 8 contains the principle that HBM and associated data should be anonymised[77] if possible for the concerned research activities. A researcher, who wants to use HBM and associated data in an identified[78], coded[79] or linked anonymised[80] form, should justify such use.

5.2.4 Consent

Article 10, §2 provides that the information and consent to obtain HBM for research should be as specific as possible with regard to any foreseen research use and the choices that the donor can make in this respect.

Article 12 stipulates that HBM removed for purposes other than storage for research (called residual HBM) should only be made available for research with the appropriate consent of the donor or an authorization of his representative. HBM can only be used without a consent or authorization if contacting the donor is not possible with reasonable efforts. There should also be an independent evaluation of the fulfilment of the following conditions: (*a)* the research addresses an important scientific interest; (b) the aims of the research could not reasonably be achieved using HBM for which consent can be obtained; and (c) there is no evidence that the person concerned has expressly opposed such research use.

Article 15 confirms that the donor has the right to withdraw or alter the scope of the consent for the storage of identifiable HBM for research purposes. It further confirms that such decision should not have any negative consequences for this donor, in particular regarding the right to medical care. When identifiable HBM are stored for research purposes only, the donor should have the right to request the destruction or the anonymisation of the HBM. These rights only apply to identifiable HBM, since it is no longer possible to link anonymised HBM to a specific donor.

Article 21 stipulates as a general rule that HBM should only be used within the scope of the consent given by the donor. Whenever a researcher wants to use identifiable HBM for a purpose that does not fall within the initial consent, he should make reasonable efforts to obtain a new consent. In case it would not be possible to obtain a new consent, the HBM could only be used for a new research purpose after an independent evaluation of a number of conditions. Unlinked anonymised HBM can be used in research without an explicit consent on the condition that the donor did not object to such use prior to the anonymisation of the HBM.

---

[77] HBM is considered 'anonymised' if does not allow, alone or in combination with associated data, with reasonable efforts, the identification of the person concerned (art. 3, ii).
[78] HBM is considered as 'identified' if it allows, alone or in combination with associated data, the identification of the person concerned directly (art. 3, i).
[79] HBM is considered as 'coded' if it allows, alone or in combination with associated data, the identification of the person concerned through the use of a code and if the user has access to such code (art. 3, i).
[80] HBM is considered as 'linked anonymised' if it allows, alone or in combination with associated data, the identification of the person concerned through the use of a code and if the user does not has access to the code and the code is under control of a third party (art. 3, i).

5.2.5 Information in relation to the collection of HBM and data and the access conditions

Article 14 provides that one should specify (a) the person and/or institution responsible for the collection, (b) the purpose(s) of the collection; (c) the conditions governing access to and use of samples; (d) quality assurance measures.

5.2.6 Independent examination of access requests

Article 24 stipulates the obligation to conduct an independent examination of the scientific merit, the importance of the aim and the ethical acceptability of a research project.

5.3 Overview of the most important modifications suggested in the Working Document

5.3.1 Protection of personal data

Appropriate security measures should be taken to ensure the confidentiality of any information of a personal nature. These measures should ensure confidentiality at the time of removal, storage, use and, where appropriate, transfer of biological materials (art. 8).

5.3.2 Public information

Article 9 provides that Member States "should take appropriate measures to facilitate public access to general information on the nature and objective of research collections and on conditions relating to the obtaining, storage and use of HBM for research purpose."

5.3.3 General rules on use of HBM and data in a research project

Article 17 § 1 stipulates that research on HBM and data should only be undertaken if it falls within the scope of the consent or authorisation given by the donor, in particular the consent given to remove and/or store HBM and data for future research.

Article 17 § 2, i) stipulates that a *new consent or authorization* should be sought if the proposed use of the *identifiable* HBM (residual and non-residual) and data in a research project do not correspond to the scope of the prior consent or authorization. Sufficient efforts should be made to contact the donor and attempt to obtain a new consent. In case the donor expressed the wish not to be contacted, such wish should be respected. Unfortunately article 17, § 2 does not specify what should happen when one does not have clear information on whether the donor explicitly expressed the wish not to be contacted.

Article 17 § 2, ii) stipulates that, in case the attempt to contact the donor proved unsuccessful, the HBM can only be used in a research project, when they have been subjected to an independent evaluation. This evaluation could be done by a REC for instance, which would evaluate the fulfilment of the following conditions: (a) sufficient efforts have been made to contact the donor; (b) the research addresses an important scientific interest and is in accordance with the principle of proportionality; (c) the aims of the research could not reasonable be achieved using biological materials for which consent or authorization can be obtained*;* (d) there is no evidence that the donor expressly opposed such research use.

Article 17 § 3 stipulates that anonymised HBM and/or data may be used in a research project provided that such use does not violate any restrictions placed by the donor prior to the anonymisation of the HBM and/or data and subject to authorization provided for by law – for instance by a REC. This provision provides a possibility to apply presumed consent for the use of *anonymised* HBM and/or data.

5.3.4 Availability of results

Art. 19 § 1 stipulates that on completion of the research, a report or summary should be submitted to the REC or the competent body. Art. 19 § 2 stipulates that appropriate measures should be taken to make the research results public within a reasonable timeframe.

5.3.5 General principles in relation to governance of collections

Article 20 § 2 provides that the purpose(s) of collections should be specified and that collections should be governed on the basis of the principles of transparency and accountability.

Article 20 § 7 stipulates that information about the management and use of the collection should be made available to the donors and should be regularly updated.

Article 20 § 8 stipulates that the conclusions of research should be publicly available.

Article 20 § 9 requires the annual publication of reports on past and planned activities and access to the collection by third parties.

5.3.6 Access

Article 22 stipulates that clear conditions governing access to, and use of, HBM should be established. Member states should furthermore take measures to facilitate appropriate access by researchers to collections of HBM and data. Access policies should include arrangements for oversight of access and transfer procedures. Finally appropriate access mechanisms should be developed to maximize the value of collections. These mechanisms should include traceability of the uses granted by the collection. It is unclear how the different terms used in article 22, namely conditions governing access, access policies, access arrangements, access mechanisms, … relate to each other. It would be more transparent to define the different terms, for example in the explanatory memorandum.

5.3.7 Oversight

Article 24 stipulates amongst others that each collection of HBM and data should be subject to an independent oversight; such oversight should include amongst others the publication of reports on past and planned activities, including information on access by third parties.

6 Comparison of the access conditions formulated at the international level, the level of the Council of Europe and the Belgian level

The section compares the most important rights and obligations of custodians, applicants and – to a lesser extent – donors in relation to access to biobanks. Those rights and obligations were found in the different legal documents studied at the international level, the level of the Council of Europe and in Belgium. One should, however, keep in mind that the international normative instruments and Recommendation 2006(4) are not legally binding in Belgium. They can however be considered an important inspiration for the development of a legal framework in relation to access to biobanks.

6.1 Aims, activities and policies of biobank

The legal instruments that have been studied at the international level and at the level of the Council of Europe, suggest that an independent REC should review the establishment, the activities and/or access to biobanks (best practice 1.2 of the OECD Guidelines; § 19 ESHG Recommendation; art. 24 of the Working Document[81] of the Committee of Bioethics).

The Belgian Act on HBM provides that a REC should provide (in the future) a positive advice on the activities and aims of the biobank (future article 22, § 1, section 5) and that the establishment of a biobank should be notified to the Medicine Agency (future art. 22, § 1, first section). Furthermore, a REC has to provide a positive advice on the secondary use of HBM and the specific aims of such use (art. 21). One could argue that the Belgian Act on HBM to a large extent provides the review by an REC as suggested by the international normative instruments. However, it is not certain how the REC and the FAGG will perform the independent oversight of biobanks, since the rules in this respect need to be published in an executive Royal Decree.

6.2 Custodianship

The OECD Guidelines suggest that biobanks should develop and maintain clearly documented operating procedures and policies for the different operations including access conducted in the framework of the biobank (principle 1.F. OECD Guidelines)

The Belgian Privacy Act and the Act on HBM do not contain any specific provisions in relation to the development of operating procedures and policies including access of biobanks. Considering the fact that many different types of biobanks exist, it is doubtful whether the national legislation should contain detailed provisions in this respect. It might be preferable to address this topic in specific access arrangements.

The Belgian Act on HBM, the Belgian Privacy Act, the OECD Guidelines, the Recommendation 2006(4) and the proposal in the Working Document do contain several rights and obligations of the custodian of a biobank. The custodian of a biobank should take into account those rights and obligations, when he/she develops access arrangements and/or operating procedures. The requirement to obtain a positive advice of an Ethics Committee in relation to the aims and activities of

[81] The Working document on 'research on biological materials of human origin' was published by the Committee on Bioethics – an intergovernmental body within the Council of Europe – on 18 March 2014

the biobank might for instance have an influence on how the biobank develops its operating procedures and access arrangements.

6.3 Evaluation of requests for access to HBM and data for research purposes

The different international/European legal frameworks applicable to biobanks agree that the use of HBM in biomedical research should be subject to a review and/or positive advice of a REC. The international normative instruments and the Working Document of the Committee of Bioethics contain an important number of additional principles on the development of policies, procedures and mechanism to evaluate request for access to HBM and data. The legislation applicable in Belgium does not provide anything in relation to the development of access policies, procedures and mechanism. One might argue that this could be regulated via access arrangements developed by biobank initiatives.

However, the Belgian Act on HBM does stipulate a limited number of rights and obligations of custodians that are suggested in the international normative instruments. Article 2, 27° provides that the custodian of a biobank will have the obligation and the right to decide on the allocation and use of HBM for research purposes. The custodian will also have to ensure that the informed consent of the donor is respected (art. 15 and art. 22 § 3). Finally the custodian will have to make sure that a REC provides a positive advice on the secondary use of HBM and the specific aims of such use (art. 21).

The international normative instruments formulate a number of additional conditions on how the custodian should exercise his right to decide on the allocation and use of HBM. Although the Helsinki Declaration and the OECD Guidelines are not legal binding in Belgium, we are of the opinion that custodians of biobanks should take those additional conditions into account in the development of access arrangements. We would like to refer in this respect, for instance to the obligation "*to ensure that any stratified access conditions and fees are fair, transparent and do not inhibit research*" (best practice 7.4 OECD Guidelines).

6.4 Intellectual property and commercialization

The OECD Guidelines suggests that a biobank should develop a policy in relation to the commercialization of HBM and data and in relation to intellectual property rights (IPR) (principle 9.D-E OECD Guidelines).

Recommendation (2006)4, the Working Document and the Belgian legal framework applicable to access to biobanks do not contain any provisions on policies.

The UNESCO Declaration, Recommendation 2006(4) – and the new provisions in the Working Document – and the Belgian Act on HBM confirm the generally accepted principle that one should not generate profit on HBM.

Article 6 of the Belgian Act on HBM stipulates that the donor cannot receive any financial or material advantage for the donation of HBM. It furthermore stipulates that the custodian of a biobank cannot pay or receive any material compensation for the transfer, procurement and receipt of HBM that has not been subject to any transformation. The donors and custodians can only receive a reimbursement

of costs caused by the donation, the removal and operations conducted on the HBM. Unfortunately there are no guidelines on how to calculate the costs of a biobank. This implies that biobanks have a certain discretionary power to calculate those costs.

The applicable framework in principle prohibits access fees that would give rise to financial gains. Biobanks can only recover their costs in relation to the collection and provision of HBM and associated data. However, biobanks can charge additional fees for other services. It is unclear to which extent those additional fees could give rise to financial gains.

6.5 Sharing in the advancement of scientific research and its benefits

The Universal Declaration of Human Rights states that everyone has the right to share in scientific advancement and its benefits. The OECD Guideline for Human Biobanks and Genetic Research suggests that a biobank should develop a policy on the sharing of benefits.

Until this day, no legally binding document has stipulated the possibility to share in the advancement of scientific research and its benefits. The previous chapters revealed that no consensus exists on how to share the benefits of scientific research. That is why we would suggest that such sharing should not be regulated via binding legislation. Biobanks could address this topic in their access arrangements in consultation with the different concerned stakeholders.

6.6 Sharing and returning of research results

The Helsinki Declaration and the OECD Guidelines formulate an ethical obligation for researchers, sponsors, editors, publishers and custodians of biobanks to disseminate the results of research studies. The OECD Guidelines suggest that a biobank should develop a policy on whether and how the results of research and analyses carried out using HBM and data stored in biobanks should be returned to the biobank. It stresses the need to develop a policy on how to incorporate them into its databases and on how to manage access to such results for further research. Finally article 20 § 8 of the Working Document stipulates that the results and conclusions of the research project should be publicly available within a reasonable period of time.

The binding legislation in Belgium does not provide anything in this respect. We would argue that biobanks should develop a policy in this respect in their access arrangements; they would preferably involve the different concerned stakeholders in the development of such policy.

6.7 Protection of personal data

The different legal frameworks studied in this chapter stress the importance of protecting the privacy and the personal data of the donors. Recommendation 2006(4) – and the new provisions in the Working Document – and the Belgian Privacy Act stipulate specific provisions on the processing and use of personal data in the framework of research projects and in the framework of a biobank. One could therefore argue that the Belgian Privacy Act provides a clear legal framework on the protection of personal data.

6.8 Balancing the rights and interests of the donor with the freedom of research

A number of international normative instruments as well as the Danish Act on Research Ethics reviews stipulate the important principle that 'medical research cannot take precedence over the rights and interests of the research subject/donor' (§ 8 Helsinki Declaration, art. 10 UNESCO Declaration, principle 3.C OECD Guidelines and section 1 of the Danish Act on Research Ethics Review). The principle is however not absolute and has to be weighed against other principles, such as the 'freedom of research'.

The legal framework applicable to biobanks should aim to balance both principles. On the one hand, the interests of the donors should be protected in an optimal manner. On the other hand, one should not unnecessary hinder the possibility to use HBM and data in research projects. The optimal balance between both principles cannot be determined in a general way. Such balance can only be determined in each specific situation.

7 Danish legal framework applicable to biobanks

We do not aim to provide an extensive overview of the Danish legislation. We limited ourselves to highlight a number of legal rules specifically relevant for access to biobanks. We then compare the legal framework applicable in Denmark – a country without specific legislation on biobanking – with the legislation applicable in Belgium – a country with specific (future) legislation on biobanking.

7.1 Overview of the legal framework applicable to biobanks in Denmark

In 1999 the Danish Ministry of Interior and Health appointed a working group to identify whether specific legislation had to be created in relation to biobanks. In May 2002 the 'biobanking' working group published the "Report on biobanks – proposal for a legal regulation of biobanks within the health field" (Report no. 1414/2002)(39).

Biobanks was defined in Report no. 1414/2002 as "a structured collection of human biological material available according to specific criteria and where the information contained in the samples can be traced to identifiable persons." (38). A collection is not considered a biobank, when samples in the collection cannot be traced back directly or indirectly to identifiable persons, for example via an encryption key (39).

Report no. 1414/2002 came to the conclusion that the existing Danish legislation "is well suited to cover also biobanks, since confidentiality and safety would be secured if biobanks were considered as other collections of data, e.g. registries." Consequently no new legislation was created and biobanks are covered by the general legislation and institutions applicable to biomedical and health research, in particular: (1) the Data Protection Act[82]; (2) the Health Act[83]; (3) the Act on Research Ethics Review[84].

[82] Act n° 429 on Processing of Personal Data of July 1, 2000
[83] the Health Act n° 913 of 13 July 2010
[84] The Act n° 593/2011 on Research Ethics Review of Health Research Projects of 14 June 2011. This Act on Research Ethics Review entered into forced on 1 January 2012 and repealed a previous Act no. 402 on a scientific ethical committee system and the handling of biomedical research projects of May 28, 2003. A

7.1.1 Data Protection Act

The Danish Data Protection Act constitutes an important legal instrument for biobanks. That is because the Danish Data Protection Agency concluded in a statement of 23 February 2001 that "*collections of human biological material fulfilling the criteria to (be considered) a biobank listed by the working group may be comprised by the definition of a manual register in the Personal Data Act, cf. s. 1(1).*" This implies that the Data Protection Act does not only apply to identification data and personal data derived from HBM, but also to collections of HBM (containing personal data) (39,127).

7.1.1.1 Processing of health data for scientific or statistical purposes

The Data Protection Act considers health data – such as data included in biobanks – sensitive personal data and therefore in principle prohibits the processing of such health data.

Health data may be processed for the sole purpose of carrying out scientific or statistical studies. Condition hereto is that such studies are of significant public importance and the processing is necessary to carry out the studies (s. 10(1)). Data processed for scientific or statistical purposes cannot be processed for other purposes afterwards (s. 10(2)). This is due to the fact that the rules that apply to the processing of health data for scientific or statistical purposes are different – and less stringent – than the general rules that apply to the processing of health data for other purposes.

Health data processed for scientific or statistical purposes may only be disclosed to third parties with the prior authorization of the Data Protection Agency (s. 10(3)).

The Data Protection Act thus allows researchers to collect, process, register and use personal data for scientific purposes and transfer them to (another) researcher without an explicit consent of the data subject. This includes identification data, derived data and tissues. The researcher should first obtain the authorization of the Data Protection Agency (39).

7.1.1.2 Authorization of Data Protection Agency

The processing of personal health data requires a notification and a prior authorization by the Data Protection Agency (s. 50 (1)(1))

The processing, the collection and storage of identifiable HBM in the framework of a biobank – i.e. when the HBM is stored for a period of time that exceeds the time required to collect and analyse the HBM – is subject to a notification and authorization by the Data Protection Agency prior to any processing of such data (39). The Data Protection Agency furthermore requires that the storage and use of biobanks comply with special guidelines. One has to define a specific purpose for such storage and use (127).

translation of the Act on Biomedical Research can be found on this website: http://www.cvk.sum.dk/English/actonabiomedicalresearch.aspx

The processing of HBM in the framework of a public research project has to be notified to the Data Protection Agency. The Data Protection Agency has to issue an opinion before the processing can take place. Since 2012, the processing of HBM in the framework of a private research project no longer need to be notified to the Data Protection Agency, when the project has been approved by a research ethics committee.

HBM stored outside the framework of a biobank has to be destroyed or anonymised when the project is finished or when the HBM will not be used anymore. (127)

7.1.2 The Health Act

7.1.2.1 Consent for collection of HBM in the framework of patient care

The collection of HBM in the framework of patient care – treatment or diagnosis – requires the informed consent of the patient. The consent can be written, oral or implied and the patient has the right to revoke the consent at any moment (s. 15).

7.1.2.2 Patient's right of self-determination regarding HBM

The patient has the right to decide that HBM stored in the framework of patient care (hereafter residual HBM) cannot be used for other purposes, such as research. Such decision will be registered in the Use of Tissue Registry (s. 29(1)). When residual HBM would be used in a research project, the health professional is expected to verify, whether the concerned donor has been registered in the Registry (s. 29 (4). Only a limited number of patients made such registration[85]. When no such registration exists, the residual HBM can be used for research purposes without the patient's consent. An opt-out system thus applies for residual HBM.

In case HBM was initially collected for therapeutic purposes, the donor can opt-out for the use of such HBM for research purposes (s. 29 Health Act). Article 20 § 2 of the Belgian Act on HBM contains a similar opt-out system for the use of residual HBM – removed for diagnostic of therapeutic purposes – for scientific research purposes.

The patient can require that residual HBM is destroyed (s. 33) or returned to the patient (s. 34). In the latter case, the patient has to demonstrate that he or she has special interest in the return of the HBM. In case the HBM has been transferred to a third party, the person (initially) responsible for the storage of the HBM has to inform such third party of the request of the patient. The right to destroy or return HBM may be denied, when vital public or private interests override the patient's interest (s.33-34).

[85] The number of people that made such registration can be found on the following website: http://www.ssi.dk/Sundhedsdataogit/Registre%20og%20kliniske%20databaser/De%20nationale%20sundhedsregistre/Dodsaarsager%20biologisk%20materiale/Vaevsanvendelsesregisteret.aspx

7.1.2.3 Confidentiality and disclosure of health information by health professionals

Information about the health of individuals and other confidential information from medical records may only be disclosed to a researcher for use in a specific research project, when the national or a regional REC has approved the research project as such (not the specific disclosure of the information) (s. 46 § 1).

The REC does not need to approve a research project that does not make use of personal health data, but other personal data. In this case, the National Board of Health and Medicine has to approve the disclosure of such data to a researcher. Such information can furthermore only be used in relation to a specific research project of particular interest to society (s. 46 § 2).

Information obtained under section 46 cannot be processed for other than statistical or research purposes. Furthermore the information can only be published in an anonymous manner, i.e. that does not allow the attribution to an individual patient (s. 48).

7.1.3 The Act on Research Ethics Review

7.1.3.1 Introduction

The Act on Research Ethics Review regulates the ethical review, the approval and the follow up of health research projects that use HBM and data. It also applies to clinical trials on medicinal products and clinical investigations of medical devices.

Section 1 stipulates the general principle that "*consideration for the rights, safety and well-being of the research participant come before (/take precedence over) scientific and societal interests to gain new knowledge and investigate existing knowledge that may justify the undertaking of a research project*."

Section 1 (13) defines a Research Biobank as "*a structured collection of human biological material that is kept with a view to a concrete health research project, and which may be accessed according to defined criteria and where information bound in the biological material may be traced to individuals.*"

7.1.3.2 Review and approval by Research Ethics Committee (REC)

All health research projects in Denmark involving human beings or any kind of HBM have to be reviewed and authorized by a REC prior to starting such project (s. 14(1)). Questionnaire surveys and medical database research projects only need such authorization when the project includes HBM (s. 14(2)[86]. The REC will take into account the following criteria in granting an authorization: (1) the risks and benefits of the trial; (2) the expected benefits from a therapeutic and public health perspective; (3) the projects' scientific standard; (4) the expectations of the project's conclusions (s.18). The collection of HBM and data in the framework of a biobank – without a specific scientific aim or hypothesis – is not subject to a notification or authorization of a REC(127).

[86] Health research projects that only involve anonymous HBM collected in accordance with the applicable legislation at the place of collection should only be notified to the ethics committee system, if the research is regulated by Section 25 of the Act on artificial insemination in connection with medical treatment, diagnosis and research, etc. (s. 14(3).

The National Committee on Health Research Ethics acts as a board of appeal against the decisions of regional committees (s. 26).

7.1.3.3 Consent

A REC will only authorize a research project on the condition that the donor has given his informed consent to participate in such project and if the donor was given access to information about the content of the project and its foreseeable risks and benefits (s. 3-5 and 17). This consent requirement applies when HBM is removed for a specific research project and stored in a biobank (s. 6). When HBM stored in a biobank is not removed for a specific research project, the Data Protection Act applies.

The regional REC could waive the obligation to obtain an informed consent for medical database research projects. This is the case if the project does not create any health risk or other strain for the research subject/donor or if it appears impossible or disproportionately difficult to obtain an informed consent (s. 10)(39). A presentation of prof. dr. M. Hartlev at the Nordic Bioethics Committee Conference 'Nordic Biobank Research - Obstacles and Opportunities' of 3-4 May 2011 in Uppsala mentioned that a lot of research projects obtained a waiver to obtain an informed consent of the donor(128).

The donor has the right to revoke his consent at any moment (s. 3 (4)). A 2014 Report of the Nordic committee of Bioethics mentions in this respect that the "*withdrawal of consent has not been accepted in practice by the research ethics committees for samples collected for clinical research.*"

7.2 Comparison of legal framework applicable to biobanks in Denmark and Belgium

7.2.1 Aims, activities and policies of the biobank

The Danish Data Protection Agency conducts an important role in the oversight of biobanks. The Agency is competent to authorize (1) the processing of identifiable health data (2) the processing of identifiable HBM in the framework of a biobank; (3) the processing of HBM in the framework of a public research project; (4) the transfer of HBM stored in biobanks to other researchers (s. 10 and 50 Data Protection Act). However, this competence to deliver an authorisation only applies when data or samples can be traced back to an individual. It does not apply to anonymous HBM or data. The Data Protection Act after all does not apply to anonymous HBM or data.

The role of the Belgian Privacy Commission in the oversight of biobanks is much more limited. The Privacy Act does not contain any provisions on the processing of HBM. The Act only provides that the processing of health data is subject to a notification to the Privacy Commission (art. 17).

In Denmark, the REC has to approve the collection of HBM in the framework of a research project with a specific scientific aim or hypothesis (s. 14 Act on Research Ethics Review). The REC is not competent to approve the creation of a biobank(127).

In Belgium the REC has to provide a positive advice on the aims and activities of the biobanks and on the secondary use of HBM (future art. 22 § 1, section 5). The establishment of the biobank furthermore has to be notified to the Federal Agency for Medicine and Health products (future art. 22, § 1, section 1).

7.2.2 Custodianship

The Belgian Privacy Act and the Act on HBM attach a lot of importance to the role of the custodian of a collection of HBM and/or data. Both acts assign several rights and obligations to the custodian. These rights and obligations relate to operations conducted on HBM and associated data and to the processing of personal data for research purposes.

In the Danish Data Protection Act, the Health Act and the Act on Research Ethics Review, the rights and obligations of the custodian of a biobank are defined in a more fragmented manner.

7.2.3 Evaluation of requests for access to HBM and data for research purposes

All health research projects in Denmark involving HBM have to be reviewed and authorized by a REC prior to starting such project (s. 14(1) of the Danish Act on Research Ethics Review). A REC (or the National Board of Health) furthermore has to approve the disclosure of health information to researchers for use in a research project (s. 46 of the Danish Health Care).

Article 21 of the Belgian Act on HBM provides that an ethics committee has to give a positive advice on the secondary use of the HBM and the specific aims of such use. In the future a positive advice of an ethics committee will not be necessary for the secondary use of HBM for research purposes. This is true at the condition that the proposed use of HBM falls within the scope of the aims and activities of the biobank and the ethics committee provided a positive advice on those aims and activities (future art. 22, § 1, section 7 and 8).

7.2.4 Intellectual property and commercialization

We did not find any specific provision on IPRs and the commercialization of HBM and data in the Danish legal framework applicable to biobanks.

7.2.5 Sharing in the advancement of scientific research and its benefits

We did not find any specific provision on the sharing in the advancement of scientific research and its benefits in the Danish legal framework applicable to biobanks.

7.2.6 Sharing and returning of research results

We did not find any specific provision on the sharing and returning of research results in the Danish legal framework applicable to biobanks.

7.2.7 Protection of personal data

The Belgian Privacy Act provides that the processing of health data is subject to a notification to the Data Protection Authorities (art. 17). The Act makes a distinction between personal data initially collected in the framework of health care or personal data collected in the framework of a research project. The initial collection of personal data in the framework of the research project is subject to the

consent of the data subject to participate in the project. There is however no requirement for a specific consent to process the personal data. When a researcher wants to subsequently process and use coded or identifiable health data that was initially collected in the framework of health care, he has to notify such processing and use to the Belgian Privacy Commission (art. 3-5, 14, 16 and 18-21 of the Royal Decree of 13 February 2001). The subsequent processing of health data is only subject to a notification and not to a prior authorization of the Belgian Privacy Commission. The Health Section of the Sectorial Committee on Social Security and Health in Belgium has to authorize the transfer of health data to a third party – such as the applicant – (art. 42, § 2, 3°, of the Act of 13 December 2006 containing miscellaneous provisions in relation to health). The Belgian Data Protection Act does not contain any rules in relation tot the processing and transfer of HBM stored in biobanks.

The Danish Data Protection Act applies both to personal data and collections of HBM (containing personal data)(39,127).The Data Protection Agency has to authorize the processing of personal health data for research purposes, as well as the transfer to another researcher (s. 10 of the Danish Data Protection Act).

7.2.8 Balancing the rights and interests of the donor with the freedom of research

Section 1 of the Danish Act on Research Ethics Review stipulates the important principle that the rights, safety and well being of the research participant takes precedence over scientific and social interests in relation to biomedical research projects.

8 Conclusion

The analysis of the legal framework applicable to access to biobanks allowed us to complete the picture of the rights and obligations – drawn up at the end of Chapter 2 – held by the custodian and the applicant in relation to access to and use of HBM and data. Certain rights and obligations are clearly regulated via the different legal instruments. First, the review of biobanks by REC is stipulated in the different legal frameworks. Second, the different legal frameworks define an important number of rights and obligations of the custodian. Third, the different legal frameworks stipulate that a REC should review and approve the use of HBM and data in research projects. Fourth, there is a general consensus that one should not generate profit on HBM (as such). Fifth, the protection of personal data is regulated via binding legislation.

Others rights and obligations are insufficiently regulated via the international normative documents and the binding legislation in Belgium and Denmark. One can refer in this respect to the fact that several international normative instruments provide that a biobank should develop a policy in relation to (a) the commercialization of HBM; (b) IPRs; (c) the sharing and returning of research results; and (d) the sharing in the advancements of scientific research and its benefits. None of the international normative instruments (or the binding legislation) contain detailed provisions on how to develop such a policy. Chapter 4 will dig deeper into the question how IPRs and the ‘return and sharing of research results’ could be regulated.

The international normative instruments contain quite detailed provisions on the development of access policies, procedures and mechanism. Those provisions constitute an important source of inspiration for the development of access arrangements.

Table 7 Overview of most important rights and obligations in different legal frameworks[87]

	Belgium	International	Council of Europe	Denmark
1. Aims, activities and policies of biobanks				
A. Obligation of custodian				
Obtain positive advice of REC on aims and activities of biobank	Yes	Yes		No
Notify establishment and activities to Medicine Agency	Yes			
2. Custodianship				
A. Obligation of custodian				
Decide on allocation and use of HBM	Yes			
Obtain and ensure respect of informed consent	Yes	Yes	Yes	Yes
Ensure respect of ethical approval of research project	Yes	Yes	Yes	Yes
Ensure that aim of use of HBM is precise and relevant	Yes		Yes	
Ensure that finality of use of HBM is specified	Yes		Yes	
Conclude prior agreement for distribution of HBM	Yes	Yes		
Develop and maintain clearly documented SOPs		Yes	Yes	
Develop and maintain clearly documented access policies		Yes	Yes	
Make access policies and procedures publicly available		Yes	Yes	
Return or destroy HBM at request of donor				Yes
B. Rights of custodian				
Decide on allocation and use of HBM	Yes			
Procure, store and provide HBM for research purposes	Yes			
3. Evaluation of access requests				
A. Obligation of custodian				
Create mechanism to review access requests		Yes	Yes	
Establish clear criteria governing access		Yes	Yes	
Ensure that access is based on objective and clearly articulated criteria		Yes		
Ensure that stratified access conditions and fees are fair, transparent and do not inhibit research		Yes		
Formulate criteria for prioritizing applications		Yes		
Provide oversight of access and transfer procedures			Yes	

[87] This table provides an overview of which rights and obligations are regulated in the different legal frameworks applicable to access to biobanks. When a particular right or obligation is regulated in a particular legal framework, we indicated 'yes'. We did not indicate when a particular right or obligation is not (explicitly) regulated in a certain legal framework. Specific information on how a particular right or obligation is regulated can be found in the description of the different legal frameworks.

B. Obligations of applicant				
Obtain positive advice of REC on use of HBM in research project	Yes	Yes	Yes	Yes
Draft research protocol		Yes		
Respect informed consent	Yes	Yes	Yes	Yes
Respect ethical approval of research project	Yes	Yes	Yes	Yes
4. Intellectual Property and commercialization				
A. Obligation of custodian				
Develop policy on commercialization		Yes		
Develop policy on IPRs		Yes		
Prohibition of financial gain	Yes	Yes	Yes	
B. Rights of custodian				
Receive reimbursement of costs	Yes			
C. Obligation of applicant				
Reimburse cost of biobanks	Yes			
5. Benefit sharing				
A. Obligation of custodian				
Develop policy on benefit sharing		Yes		
6. Sharing and returning of research results				
A. Obligation of custodian				
Develop policy on returning and sharing research results		Yes		
B. Obligation of applicant				
Ethical obligation to publish and disseminate results		Yes		
Take appropriate measures to make research results public available			Yes	
7. Protection of personal data				
A. Rights of custodian				
Process personal data in the framework of biobank	Yes	Yes	Yes	Yes
B. Obligations of custodian				
Ensure protection of personal data	Yes	Yes	Yes	Yes
Notify processing of personal data	Yes			Yes
Obtain authorization of Privacy Commission/Data Protection Agency	Yes			Yes
C. Rights of applicants				
Process and use personal data in research project	Yes	Yes	Yes	Yes
D. Obligation of applicants				
Ensure protection of personal data	Yes	Yes	Yes	Yes

9 Overview of the studied legislation

9.1 Belgium

Act of 19 December 2008 on the procurement and use of human bodily material, Belgian Official Journal of 30 December 2008

Royal Decree of 28 September 2009 stipulating the general conditions that banks for HBM, intermediate structures and production establishments need to fulfil in order to obtain an approval from the Medicine Agency, Belgian Official Journal of 23 October 2009

Royal Decree of 28 September 2009 on the supervision on the compliance with the Act of 19 December 2008 on the procurement and use of human bodily material, Belgian Official Journal of 23 October 2009

Royal Decree of 28 September 2009 with quality and safety norms for the donation, removal, procurement, testing, processing, storage and distribution of HBM, to which banks for HBM, intermediate structures and production establishments have to comply, Belgian Official Journal of 23 October 2009

Royal Decree of 28 September 2009 stipulating provisions on the notification of serious adverse events or reactions in relation to HBM, Belgian Official Journal of 23 October 2009

Act of 22 August 2002 concerning the rights of patients, Belgian Official Journal of 26 September 2002

Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data, Belgian Official Journal of 18 March 1993

Royal Decree of 13 February 2001 in execution of the Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data, Belgian Official Journal of 13 March 2001

9.2 International

The Universal Declaration of Human Rights, proclaimed by the United Nations General Assembly in Paris on 10 December 1948.

The World Medical Association Declaration of Helsinki entitled “Ethical Principles for Medical Research Involving Human Subjects”

The UNESCO Universal Declaration of 1997 on the Human Genome and Human Rights

The OECD Guidelines for Human Biobanks and Genetic Research Databases (2009)

Recommendation of the European Society of Human Genetics, entitled “Data Storage and DNA Banking for Biomedical Research: Technical, Ethical and Social Issues” (2001)

9.3 Council of Europe

The Recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin

Working document on 'research on biological materials of human origin' published by the Committee on Bioethics on 18 March 2014

9.4 Denmark

Act n° 429 on Processing of Personal Data of July 1, 2000

Health Act n°913 of 13 July 2010

The Act n° 593/2011 on Research Ethics Review of Health Research Projects of 14 June 2011.

Chapter 4: IPRs in biobanking: Risks and opportunities for translational research

This chapter is based on:

Verlinden M, Minssen T, Huys H

IPRs in biobanking: Risks and opportunities for translational research.

Intellect Property Q. 2015 [Accepted for publication]

1 Introduction[88]

The worldwide focus on biobanks has increased considerably due to several reasons. Large-scale, interoperable biobanks make it possible for researchers with different backgrounds and scientific expertise to analyse large and diverse collections of biospecimen, as well as genetic, clinical, health and other personal data of the donor. Those analyses could allow them to identify novel biomarkers or to validate the clinical significance of genomic mutations. After discovering – for example – a certain gene that could correlate with the severity of a given disease or condition, researchers can use HBM to test new drug candidates that target this mutation(21).

Thus biobanks can provide a crucial platform for international and interdisciplinary cooperation. They can act “as key drivers for next generation biomarker (diagnostics) research and drug discovery”(21). Since size and quality really matters in this field, translational research increasingly requires cooperation between top quality biobanks in different countries. There has been a gradual shift from traditional closed innovation systems to more “open” and “transparent” innovation models. At the same time there were rapid technological advances and bio-pharmaceutical innovation gaps. These factors have highlighted the increasing importance of an effective establishment, governance and use of large-scale longitudinal biobanks(129). Biobanks, and in particular public biobanks, are often constructed to operate for several decennia and to be used by numerous research projects. They could potentially be used by a great variety of stakeholders with different objectives. Such stakeholders could be private companies, university researchers, bio hackers, research foundations, patient groups, governmental bodies or "hybrid" consortia in the framework of Private Public Partnerships (PPPs). This great variety of stakeholders and the increasing significance of biobanking require substantial investments in the creation, organization and maintenance of the HBM and data stored in biobanks.

This raises important organizational, regulatory and ethical questions for any type of biobank. It also raises legal questions such as how to deal with intellectual property rights (‘IPRs’) that could arise out of the creation or later use of the collected HBM and data. This is a complicated question that often involves both IPRs and contractual rules and interests. As a starting point, the IPR legislation identifies (amongst other) the subject matter and the beneficiaries of the protection. In patent law, only subject matter that is not considered as pure discoveries is patentable. The (exclusive) rights arising under IPR can then in principle be transferred by a contract. Research collaborations between stakeholders often would involve such technology- or information transfer.

It is therefore also a specific issue under which conditions a biobank could or should become (co)owner of IPRs *resulting* from the use of the HBM and data which it provided, selected and possibly processed for the specific research (so-called downstream IPRs). This entails investigating how to reach a balance between the exclusive nature of IPRs to exclude others from using protected material without consent of the owner, and the requirement of funding agencies to share as widely as possible

[88] This Chapter was written together with prof. dr. Timo Minssen (University of Copenhagen) and prof. dr. Isabelle Huys (KU Leuven)

(with minimal restrictions) the data which result from research on the basis of HBM and associated data.

Another issue concerns the modalities and conditions for use of the data derived from the biobank. It pertains to the choice between an "open" and "closed" collaboration model or a combination thereof. Even though there are built-in tensions between the rules of IPR and the norms underpinning the principles of "openness" and "data sharing", it is important to bear in mind that IPRs do not imply the establishment of closed collaboration models. Instead, right holders could use the IPRs provided to them to find the right balance. This balance lies somewhere in what has been described as "the spectrum between free use of knowledge by anyone for any purpose and exclusive use by one entity for its own use"(130). The mere acquisition of IPR does not necessarily imply any specific modalities for rights administration and user-generated solutions. Instead it necessitates to make decisions and agreements about the way IPRs are/can be used, and to be aware of the consequences of the different choices(129).

Developing biomedical treatments or diagnostics can be very costly and industry involvement is thus often essential. Therefore, an appropriate balance in the user modalities of IPRs appears particularly important within the area of translational medicine. In order to obtain the necessary knowledge to develop new drugs (or new uses of existing/approved drugs), access to large-scale biobanks is crucial. For this reason (international) cooperation between different institutions is needed. The industry has realized that the development of truly innovative biologics and "cutting edge" personalized therapies is complex and difficult to achieve within the traditional "closed innovation" model. New strategic partnerships with competitors, smaller specialized biotech companies or with governmental institutions through Public Private Partnerships (PPPs) are often necessary to develop breakthrough-drugs. This has encouraged several innovator companies to support the current shift towards more transparency in the pharmaceutical sector. In addition to regulatory responses and initiatives from authorities[89], the drug industry has initiated their own transparency projects. These include biobank-initiatives with a various level of transparency.[90] However, due to the immense risks and costs associated with pharmaceutical R&D and clinical trials, the industry and investors would – at least at some stage – presumably require a certain type of exclusivity. This could e.g. be achieved through IPRS and licenses, regulatory exclusivities or trade secrets. Therefore, determining the right balance between openness and exclusivity is particularly decisive but also difficult here.

So far only a limited number of studies have delivered in-depth insights in strategies and policy choices with regard to IPRs in biobanking. The inherent complexity involving many areas of expertise and stakeholders, probably explains why. Previous studies focused on the potential negative impacts and risks of IPRs in the context of biobanking(131). Only a few projects highlighted the opportunities and potential benefits of user-generated solutions and proper governance of IPRs in

[89] This shift has not only resulted in data disclosure provisions in the new European regulations on clinical trials but also to – arguably rather cautious - transparency initiatives by the FDA and the EMA.
[90] See e.g. Astra Zeneca's transparency program at: http://www.astrazeneca-us.com/responsibility/corporate-transparency (last visit 10 May 2014).

biobanking(112,132). Moreover, there seems to be a far too narrow understanding of the concept of IPRs in the academic debates on biobanking. After all, IPRs are not only about the protection of private interests. The underlying rationales of intellectual property intend in fact to stimulate innovation and to promote technology transfer under fair conditions. The debate on IPRs and biobanking is furthermore often narrowed down to patent rights, while several other types of IPRs could be relevant for biobanking. Another misconception is that "IP might not be so relevant for biobanks" and would only constitute a hurdle for access to biobanks.

Against this background, the paper aims to provide an overview and analysis of the most relevant IPRs in biobanking. It further discusses the risks and opportunities associated with the identified IPRs for an effective use of biobanks in translational research and innovation. In pursuing this goal it will often be necessary to distinguish between different types of biobanks. Different types of biobanks exist, depending on their design and purpose, as well as on the perspectives of multiple stakeholders. We decided to focus on biobanks collecting human samples.[91] We therefore define for the purpose of this paper "a biobank" as "an organized collection of human biological materials and associated information stored for one or more research purposes"(26).[92]

To achieve our objectives, we *first* identify the types of IPRs that we consider as most relevant in relation to 'access to biobanks'. We also briefly describe the basic requirements and rationales for receiving IP protection. We then define potential right holders and ownership options, and explain the legal effects of the protection granted.

Section 2 specifies potential challenges in finding a balance between an open and a close collaboration model. We elaborate on possible tensions between the exclusive nature of IPRs and obligations posed by funding agencies and "open innovation" partnerships to share the results from research on and with biobank material and data. Moreover, we discuss how rights of donors or patients may influence the possibility to obtain IPRs on technologies developed with biobank material and data.

Taken into account the above, *section 3* will analyse and discuss potential strategies and options to stimulate the exchange of HBM, data and research results. It will also look into the question of how to address, govern and manage IPRs directed to biobank material and data. We investigate in more detail if, and under which conditions, a biobank could/should become co-owner of upstream and downstream IPRs.

This will ultimately allow us to draw conclusions in *section 4*.

[91] These can be distinguished by various categories depending on purpose and design. They include i.a. population-based biobanks, disease-oriented biobanks, case control biobanks, tissue biobanks and biobanks for clinical trials. These basic categories can be divided into specific sub-groups, such as stem cell biobanks, tumour biobanks or cord-blood banks.

[92] Note that collections of non-human material, such as plant, animal, microbe, environmental, may also be described as biobanks but this is less relevant for the purposes of this paper. For a more detailed and generally applicable definition of biobanks cf. (6).

2 Different IPRs relevant for access to biobank

2.1 Definition, nature and different forms of intellectual property rights

Previous debates on IPR and biobanking often started from a narrow focus of the concept of IPRs. Some authors limited their analysis to patent rights, while several other types of IPRs could be relevant for biobanking. After all, the term 'intellectual property rights' ('IPRs') is used to describe several distinct (exclusive) rights that are granted to creators of intellectual creations, i.e. creations of the mind, such as a scientific article or an invention(110). Other IPRs that can be relevant in the biobank context are copyright, *sui generis* databases protection (in Europe), trade secrets, trademarks and data exclusivity.

Previous publications almost exclusively focused on the potential negative impacts and risks of IPRs for biobanking. They do not take into consideration that IPRs can be used/exercised in many different ways. An IPR can be described as a negative right to prohibit others from using a protected creation without the authorization of the IPR holder. However, IPRs can also be used to protect and balance the interests of the different parties involved. Several studies confirmed that IPRs are often not exercised in a manner that prevents others from using IPR-protected creations to develop new technology or knowledge(132). In some cases (see hereunder) IPRs holders grant third parties the right to use their creations under reasonable (market) access fees and conditions.

Several authors focus on the distinction between the 'closed/exclusive' IP world and 'open/shared' biobank world(131). However IPRs are not only about the protection of private or commercial interests. In fact, IPRs are granted as incentives and rewards to authors and inventors that develop new products or intellectual works that may benefit the society as a whole(110). It allows them to recover their development costs(133).

Finally some feel that negotiations on IPRs form an additional hurdle(16,134). Although negotiating about IPRs can take some time, it can still be worthwhile to have clear contractual arrangements on how to manage IPRs that could arise from the use of HBM and data in research projects. This could avert situations where biobanks, funders or researchers are no longer allowed to use research results or analyses carried out using HBM and/or data that are stored in publicly funded biobanks. Furthermore clear contractual arrangements on IPRs could avert further discussions or litigation between different actors that provided a significant contribution to creations that can be protected by IPRs(134).

The relevance of particular IPRs depends on the particular phase in the 'lifetime' of a biobank(134). During the *creation phase,* the biobank sets up the necessary infrastructure, such as technical equipment and software, and databases to store HBM and data. The biobank develops policy documents and templates, operational procedures and often uses a particular name or logo for its identification. Websites may be created as well as online tools for applicants or managers to communicate with the biobank. During the *collection phase* human biospecimen and data from different resources are collected and arranged – according to certain (selection) criteria – in a biobank and/or database. Often HBM are further processed (e.g. DNA extraction from blood samples)

according to certain protocols. Software may be developed to conduct and analyse interviews with participants and to process the collected data(16). Researchers that are interested in some of the collected HBM and data can apply for access to the collection (*access phase*). Once the application for access has been approved, the applicant/researcher can use the HBM and data in a research project *(research phase).* Finally the use of the HBM and data in the research project may lead to products or services, such as new diagnostic tests, therapies or medicine (*valorisation phase*) (16). This chapter focuses on the so-called 'access phase'.

2.2 Copyright protection

Copyright protection is offered to literary and artistic creations (art. 2 of the Berne Convention[93]), such as scientific and technical texts, reports, images, software, the "look and feel" (appearance/design) of a database or the content and form of a website. Creations are only protected by copyright if one can demonstrate that the creation is original, i.e. it bears the personal stamp of the author and draws from the intellectual effort of the author(135–137). This implies for instance that the design of the database should not be merely determined by functional features, such as the organization per type of HBM or data. It should not merely contain a list of factual information without a special manner of organizing or representing the information(137). Copyright furthermore does not offer protection to an idea in itself, but only to the concrete expression/form of the idea. If an idea can take shape in various ways, it is only the concrete expression of the idea that is protected under copyright(136,137).

During the access, research and valorisation phase, copyright could be held in relation to the appearance or design of the database of HBM and data(137) or the website[94] that provides virtual access to the collection of HBM and/or data. One can furthermore hold copyright in relation to data and publications that result from the use of HBM and/or data used in the framework of a research project. Copyright protection allows the custodian of the biobank to decide who has access to the collection of HBM and/or data and to which extent a third party could use a similar structure to represent its collection.

If a biobank or elements within the biobank are protected by copyright, the 'custodian' of the biobank could prohibit third parties from copying those elements that are protected by copyright(137). In case the biobank would allow a third party to use those elements, it has the right to require the third party to make reference to the original creator of those elements. The copyright holder cannot however prevent a third party from reproducing or communicating (part of) the creation for the sole purpose of illustration for teaching or scientific research.

[93] Berne Convention for the Protection of Literary and Artistic Works of September 9, 1886
[94] A sui generis data base right, as explained hereunder, could protect the investment in the content of the database.

Copyright protection is obtained from the moment the creation is disclosed and does not require the fulfilment of any formalities or any registration. The protection in principle continues for 70 years after the natural person (/author) is deceased (art 2 of the EU Directive on the term of protection of copyright and certain related rights[95])(136,137).

2.3 *Sui generis* data base protection

In the European Union the investment in the content of a database (in other words the data in the database) may be protected by a special "database right"(136,137). Some argue that collections of HBM that are organized in a systematic or methodical way, could be considered as a database as defined in article 1, § 2 of the Database Directive (131,137).

One should furthermore demonstrate that a substantial investment - in money, time, effort or energy - has been made to obtain, verify or present the content of the database (art. 7 of the Database Directive). This investment must relate specifically to the creation of the database and cannot take into account the investments made in order to create the data. It is important to remember that database rights do not provide any protection for the creation of the elements included in the database. The protection only relates to the investment made in the acquisition and collection of the data(136,137).

During *the access phase,* the biobank can invoke its *sui generis database rights* to determine the conditions applicable to access and use of the collection of HBM and data. It can use its right to only allow access to applicants that successfully submitted an application for access to the collection. The biobank can ensure that applicants initially only obtain access to evaluate the usefulness of the collection for the research project and subsequently to use the HBM and data within the scope of the access applications. Applicants can be prohibited from extracting substantial parts of the biobank to create their own collections of HBM and data (136,137).

Different parties that invested or contributed to the establishment and development of the database could claim simultaneously *sui generis rights* on the whole or parts of the biobank(137). These parties could be the funders, the persons and institutions that establish and operate the database, but also individual researchers or clinicians that made a substantial contribution to the collection of HBM and the collection and/or generation of data stored in the database(129). That is why it may be important to have clear arrangements on whether and under which conditions different concerned parties could hold *sui generis database rights* and how the different stakeholders will be able to use the collection of HBM and data(119,137).

The protection of the *sui generis* database right starts from the date when the database is completed or made publicly available and does not require the fulfilment of any formalities or any registration. The protection continues for a period of 15 years (art. 10 of the Database Directive). Whenever the database is modified in a substantial way and this modification requires a substantial investment, a new term of 15 years starts for the new form of the database. Biobanks could theoretically enjoy an

[95] DIRECTIVE 2006/116/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on the term of protection of copyright and certain related rights

eternal protection, since the collections of HBM and data periodically undergo substantial updates (136,137).

2.4 Trademarks

Trademark protection could be obtained for the following signs: (a) a word or combination of words (slogans, domain names or the name of a company, a product or a service, etc.); (b) drawing, figures, shapes, smells and even sounds (art. 2 of the EU Trademark Directive[96]).

The biobank could register the name, the logo or the slogan of the biobank or its products or services as a trademark(131). The biobank could also register a trademark in relation to the name or the logo of the database or software it developed. The UK Biobank is an example of this. It registered the name “UK Biobank” and the logo of the biobank as trademark for amongst others scientific, technological and medical services, research in the fields of medicine and the design and development of computer hardware and software[97].

Trademark protection can only be obtained for signs that fulfil a number of conditions (art. 3 of the EU Trademark Directive). First it has to be demonstrated that the sign can be represented graphically. Since it is difficult to provide a graphical representation of a smell, few trademarks are obtained in relation to such ‘sign’. Furthermore, the sign must have a sufficient distinctive character. This implies that the sign must be appropriate to distinguish the goods or services of a particular undertaking compared to those of other undertakings. The sign should not merely describe the goods or services for which the trademark is requested. Thus, one can obtain a trademark registration for the word "apple" in relation to computers, but not for the fruit apple.

Trademark protection requires a successful application to a national or regional trademark office (such the (European) Office for Harmonization in the Internal Market ("OHIM") or the International Bureau of the WIPO. Such trademark office will evaluate whether the concerned sign fulfils the requirements to be registered as a trademark. The applicant has to indicate in the trademark application the goods or services for which he/she wishes to obtain trademark protection(136) (138).

During the access, research and valorisation phase, the biobank could invoke its trademark rights to oblige the researcher to explicitly mention the name, logo or slogan whenever the goods or services of a biobank are used. It could also oppose the use of its trademark for goods or services that are not provided by the biobank (art. 5 of the EU Trademark Directive).

The biobank cannot in principle oppose the use of an identical or similar trademark, if such use is necessary to indicate the intended purpose of the goods or services (art. 6 of the EU Trademark Directive). For example, it is unlikely that the UK Biobank could oppose the fact that another biobank in the United Kingdom would describe its biobanks using the terms ‘UK’ and ‘Biobank’ in combination with another sign, such as the UK DNA Biobank.

---

[96] DIRECTIVE 2008/95/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 October 2008 to approximate the laws of the Member States relating to trade marks

[97] See: http://www.trademarkia.com/uk-biobank-77806660.html and http://www.trademarkia.com/biobank-uk-77806839.html (last consulted on 10 December 2014)

The registration of a sign as trademark offers a protection of 10 years starting from the moment of the application or registration of the concerned sign (art. 46 of the Community Trademark Regulation). However, the trademark registration may be renewed for unlimited periods of 10 years and thus the trademark protection could in principle be obtained for an indefinite period of time.

2.5 Trade secrets

The protection of trade secrets can be considered an important and complementary tool to protect information, ideas and knowledge that required substantial investments.

The way of establishment or operation of a biobank could have an important impact on the quality of the HBM, associated data and the services provided by the biobank. It could therefore be considered a valuable trade secret, Trade secrets could for instance relate to the (systematic) approach chosen to collect, store, label, process and track HBM and data or to the algorithm used to analyse data collected in the framework of the biobank. The biobank could also hold trade secrets in relation to standard operating procedures and protocols, digital templates, working models and construction of databases.

Biobanks may have invested considerable amounts of time and funds in such trade secrets and may want to avoid that a third party could simply copy and apply them. Researchers that access collections of HBM and data could be requested to commit themselves to respect the confidentiality of the trade secrets developed by the biobank. A third party would not only have to copy the database content or structure or software, but would also need access to certain confidential knowhow or information to establish and operate the database or software in an optimal manner. In this respect, trade secrets could offer an additional protection of databases or software developed by the biobank.

Currently no harmonized definition of a ‘trade secret’ exists. Nor does the European Union have a harmonized protection system for trade secrets. The member states of the European Union offer different levels of protection via different legal instruments, such as unfair competition, contract and criminal laws.

In November 2013 the European Commission published a proposal of EU “Directive on the protection of undisclosed know-how and business information (i.e. trade secrets) against their unlawful acquisition, use and disclosure”(139) (hereafter Proposal Directive). On 26 May 2014, the Council of the European Union published a modified text of the Proposal Directive (140). The Proposal of Directive suggests a harmonized definition of trade secrets information, in particular information that meets 3 requirements: *(a) is secret in the sense that it is not, as a body or in the precise configuration and assembly of its components, generally known among or readily accessible to persons within the circles that normally deal with the kind of information in question; (b) has commercial value because it is secret; (c) has been subject to reasonable steps under the circumstances, by the person lawfully in control of the information, to keep it secret (art. 2, §1 (1))*.

The future directive would also protect compilations of publicly available information that is combined in such a manner that it becomes commercially valuable and is not yet known within the concerned sector (art 2, § 1 (1) (a)). One could for instance think of combining characteristics of different known manufacturing process to optimize the production of a certain product.

Trade secrets are only protected as long as they remain secret. Once the underlying information is publicly available, anybody can use the knowhow or information (110).

Protection is only offered to trade secrets that have a certain commercial value (art 2, § 1 (1) (b)) and not to information that is trivial, vague or publicly available(133). The trade secret holder does not, however, have to demonstrate that the trade secret constitutes an innovative step or is novel or original.

The person or organization that claims protection of its trade secrets has to demonstrate that it has taken reasonable steps to protect the confidentiality of the trade secret (art 2, § 1 (1) (c)). Such reasonable steps could consist of ICT protection of confidential information or confidentiality agreements (i.e. non-disclosure agreements) with third parties that need to have access to the trade secrets.

Trade secrets offer protection for knowhow and business information that cannot be protected by IPRs. This could, for instance, be an invention that does not fulfil the requirements to obtain patent protection, in particular novelty, inventive step or industrial application (110)(133). The application of an existing technology in a new sector could constitute a trade secret, even when such application seems obvious.

Trade secrets also protect knowhow or information that is not described in a patent application but that remains secret and is crucial to optimize the use of an invention. Patent holders often decide not to disclose such knowhow or information in the patent application because this would enable other parties to use the knowhow or information after the expiration of the patent. The patent application needs to contain sufficient information to be able to 'enable' the invention (Art. 84 of the EPC), but it does not need to contain all information necessary to apply the invention in an optimal manner.

One of the advantages of trade secrets is that the protection can in principle last in perpetuity, while other conventional types of IPRs – except for trademark rights – offer protection for a limited period or time. However, the protection stops as soon as the information, protected by the trade secret, becomes publicly available or looses its commercial value (110,141).

Trade secrets provide protection without the fulfilment of any formalities or registration at an official authority. The costs to register, maintain and defend other types of IPRs – such as patents – can be quite substantial. Trade secret protection however, does not require any additional investment(141). One could consider the possibility of depositing a text describing the trade secret at a notary or for instance in an i-DEPOT at the Benelux Office for Intellectual Property[98] (110). This would enable the

[98] www.boip.int

trade secret holder to prove in a future conflict the existence of the trade secret and the date when the trade secret was developed and described. However, depositing a trade secret does not grant the trade secret holder any exclusive rights.

Article 3 of the Proposal Directive defines the unlawful acquisition, use and disclosure of trade secrets. The acquisition of trade secrets is considered unlawful when carried out without the consent of the trade secret holder. This could happen by: (a) unauthorised access to, copying or appropriation of any documents, objects, materials, substances or electronic files containing the trade secret or from which the trade secret can be deduced; or (b) any other conduct which, under the circumstances, is considered contrary to honest commercial practices (art. 3, § 2).

The use or disclosure of a trade secret shall be considered unlawful whenever carried out, without the consent of the trade secret holder, by a person who (a) acquired the trade secret unlawfully; or (b) is in breach of (i) a confidentiality agreement or any other duty to maintain the secrecy of the trade secret; or (ii) a contractual or any other duty to limit the use of the trade secret (art. 3, § 3). The acquisition, use or disclosure of a trade secret shall also be considered unlawful whenever a person, at the time of acquisition, use or disclosure, knew or should have known that the trade secret was obtained directly or indirectly from another person who was using or disclosing the trade secret unlawfully (art. 3, § 4). Finally the production, offering or placing on the market and the import, export or storage of infringing goods is considered unlawful, when a person carrying out such activities, knew or should have know that a trade secret was used unlawfully.

Article 4 (1) of the Proposal Directive provides a number of exceptions. The acquisition of trade secrets shall be considered lawful when the trade secret is obtained by: (a) independent discovery or creation; (b) observation, study, disassembly or test of a product or object that is publicly available or that it is lawfully in the possession of the acquirer of the information (i.e. reverse engineering); (c) any other practice which, under the circumstances, is in conformity with honest commercial practices. The independent discovery or creation of product that contains the trade secret is thus not unlawful. One, however, has to demonstrate the independent and lawful nature of the discovery or creation.

Article 4 (2) of the Proposal Directive contains another exception. The alleged acquisition, use or disclosure of the trade secret will not be punishable, if such activity is carried out in any of the following cases: (a) for making legitimate use of the right to freedom of expression and information; (b) for the purpose of revealing an applicant's misconduct, wrongdoing or illegal activity; (c) the trade secret was disclosed by workers to their representatives as part of the legitimate exercise of their representative functions; (d) for the purpose of protecting a legitimate interest. The possibility to acquire, use or disclose trade secrets in the framework of the right to information could lead to some conflicts. Think of someone using the right to freedom of expression to acquire access to data submitted to regulatory authorities in the framework of the registration of medicinal products.

Trade secret protection relates to the content of the protected information, knowhow or idea. It does not relate to the way the trade secret is expressed. The trade secret holder, therefore, cannot only object to the use of identical drawings or designs, but also to drawings or designs that represent the

same information or knowledge(141). The trade secret holder cannot, however, object to the fact that a third party would develop independently identical production process or algorithms(141).

2.6 Patents

In Europe, the four essential pre-conditions governing the patentability of inventions under the European Patent Convention (EPC) are laid down in Article 52(1) EPC. It reads: 'European patents shall be granted for any *inventions*, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application'. Thus, in a first step, in order to be patentable, there needs to be an invention. Thereafter, that invention has to fulfil the patentability requirements of novelty, inventive step and industrial applicability. Article 53 EPC stipulates that "*no European patent shall be granted in respected of inventions (in case) the commercial exploitation of (such invention would be contrary to "ordre public" or morality*"[99].

The concept of 'invention' as such is not defined in the EPC. The Implementing Regulations to the EPC however, do specify that the invention must have a technical character (Rule 29(1)), that is related to a technical field (Rule 27(1)(a)) and concerned with a technical problem (Rule 27(1)(c)). It is clear from these rules that 'technicality' is a key precondition for qualification as a patentable invention in Europe(110).

Article 52(2) EPC lists exclusions which should not be regarded as inventions, if claimed 'as such' (Article 52(3) EPC), because they are abstract in nature (*discoveries*) or non-technical in nature (scientific theories or methods for performing mental acts). In Europe, whether products or processes identified in the context of biobanking are to be regarded as *inventions* eligible for patent protection, or whether they are *discoveries* or principles of nature and thus excluded from patentability, depends on the technical character related to the claimed subject matter. There must be something more than mere disclosure of a natural phenomenon(110).

Statutory, any "biological material *isolated* from its natural environment or *produced* by means of a technical process, may be the subject of an invention even if it previously occurred in nature" (Art. 3 Biotechnology Directive 98/44/EC). For human genes, the industrial applicability of the invention, meaning its function, needs to be disclosed in the patent application (Art. 5 Biotechnology Directive 98/44/EC). Thus, in principle, a cell or gene could become patentable as soon as some human intervention is needed to isolate such cell or gene from its natural environment by any technical means and as soon as the cell or gene (accompanied by its function) can be properly characterized by either the process by which it is obtained (product-by-process), by its structure or other means (110). Furthermore, processes of manipulating HBM (such as isolation, characterisation or storing) may be patentable inventions. Under European law, only a very thin line separates *inventions* from *discoveries*.

[99] We will not go deeper into this exception, since this chapter is focused on access to biobanks and not on the commercial exploitation of inventions. The thesis of Sarah Panis (110) studied this issue in detail in relation to the patentability of stem cells.

Therefore, it is useful to investigate the second and third very important patentability requirements, namely novelty and inventive step. These are of high relevance for cells and genes of human origin. An invention can be patented only if it is new and involves an inventive step. An invention is considered to be new if it does not form part of the state of the art (art. 54 EPC). In other words, if the cells or gene as claimed in the patent have never been isolated or produced before. An invention is considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art (art. 56 EPC). The literature with respect to cells and genes is enormous and this makes it more and more difficult to demonstrate that a particular cell or gene is new or involves an inventive step.

HBM – as such – could be considered natural products isolated from the human body. Hence, most HBM – such as blood or sperm that has not been the object of a technical process (110) – stored in the biobank would probably not be the object of patent rights. Patent rights have been granted both in Europe and the US in relation to (isolated) DNA, stem cells and – most importantly – methods and particular applications useful in diagnostics and personalized medicine(110). Nonetheless, the granting of such patent rights remains much debated(142,143). A biobank could acquire patent rights in relation to innovative technology or equipment developed for the improved collection, labelling, processing, storage, tracking and retrieval of HBM and data(16), as well as for data analysis and presentations(144). The use of HBM and data from the biobank in the framework of a research project could result in patentable inventions further downstream(129). Patent rights will in principle not be granted in relation to the data resulting from the research project, as such. They will only be granted for an application of such data such as a genetic tests or a new biomarker. Patents may be applied for, for modified HBM such as differentiated stem cells, or isolated genetic sequences or methods to generate modified HBM. Granting a patent in relation to modified HBM could limit the possibilities to commercialize data, products or services that are developed on the basis of such patented HBM(145). A biobank will only be able to claim patent rights, if it demonstrates that it made an essential contribution to the invention. The mere provision, selection and/or processing of HBM and data will probably not be enough to demonstrate such inventive contribution.

One can only obtain patent protection after a patent application has been submitted to a competent patent office that evaluates whether the conditions are fulfilled to obtain patent protection.

A supplementary protection period for the product covered by the basic patent may be requested for medicinal products with a marketing authorization and a patent for the active medicinal substance[100]. The supplementary protection will last maximal five extra years.

[100] REGULATION (EEC) NO 1768/92 OF THE COUNCIL of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products

2.7 Regulatory data exclusivity

Many of the costly steps involved in biomedical research or pharmaceutical R&D are either not patentable by their nature or very likely to be invalidated in patent challenges. When the conduct of clinical trials has taken a considerable amount of time, the remaining patent protection period is sometimes also rather limited. Therefore, the European system provides for various forms of additional protection. Some of these types of protections are linked to the previous existence of patents, such as supplementary protection certificates (SPCs). Other forms of protection are completely independent from patents. These are, for instance, the protection of clinical test data through regulatory data exclusivity, regulatory market exclusivity or trade secrets. A detailed comparative analysis of the available types of regulatory exclusivities in Europe falls outside the scope of this paper. Instead we will briefly describe their most basic general features. This will allow us to ultimately discuss their relevance for biobanking.

2.7.1 Basic characteristics of regulatory data exclusivities in Europe and in the US

The EU rules governing regulatory exclusivity changed in 2005. The (new) Directive 2001/83/EC[101] and Regulation (EC) No 726/2004[102] adopted the so-called "8 + 2 + 1" year rule. According to this approach, data exclusivity applies during the first 8 years from the grant of the innovator company's marketing authorization. Following the expiration of the first 8 years period, a generic company may start to cross-refer to the pre-clinical and clinical trial data of the originator in their regulatory applications. The data exclusivity period is followed by a 2-year market exclusivity period. Therefore, generic competitors still cannot market their product for another 2 years. Following the period of 10 years (8+2) from the grant of the innovator company's marketing authorisation, the generic company may also market their product. This is, provided that the innovator product does not qualify for a further one year of market exclusivity. This additional 1-year protection could be granted in a number of circumstances. There exists for instance a 1-year additional *market exclusivity* for a new therapeutic indication for the relevant medical product that brings significant benefit in comparison with existing therapies (Art. 14(11) Reg. (EC) No 726/2004).[103] An additional 1-year *data or market exclusivity* may be available for a new therapeutic indication of a *well-established* substance, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication (Art. 10(5) Dir. 2001/83/EC). An additional 1-year of *data or market exclusivity* may be available for a change in classification of a medicinal product on the basis of significant pre-clinical tests or clinical trials (Art. 74(a) Dir. 2001/83/EC).

---

[101] DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the community code relating to medicinal products for human use, Official Journal L – 311, 28/11/2004, p. 67 – 128.

[102] REGULATION (EC) NO 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance) (OJ L 136, 30.4.2004, p. 1).

[103] For initial MA applications submitted after 20 November 2005 and authorisation of new indication within 8 years.

In addition to the 8+2+1 regime, the European system recognizes specific *sui generis* forms of protection. These aim specifically at fostering the development of specific inventions and applications that are useful for the treatment of children (*paediatric extensions*) or very rare diseases (*orphan drugs*). These may encompass dosage regimes useful for *paediatric* applications under Regulation (EC) No 1901/2006[104] (e.g. 6 months SPC extensions) and strong marketing exclusivities (10-12 years) for *orphan drugs* and *paediatric orphan drugs* under Regulation (EC) No 141/2000[105].

2.7.2 The relevance of regulatory exclusivities in biobanking scenarios

An increasing importance is given to regulatory exclusivities for innovation policy debates. It appears important that biobank operators are aware of the significance of these special "late stage" IP rights and that they address them accordingly in their guidelines and set-up. Public biobanks may not be directly involved in clinical trials and MA procedures. They should however carefully consider potential conflicts with guidelines requiring commercial users to return to the biobank research data that is derived from downstream research or clinical trials conducted with the biobank samples. It could be the intention of the relevant biobank to make the returned (clinical trials-) data publicly available to any subsequent users of the relevant biobank samples. If this subsequent user then intends to also apply for MA approval of a generic drug or wants to cross-reference to existing pre-clinical or clinical data, the medicine authorities may not accept such references due to data exclusivity. Or in other words, data exclusivity rules could undermine the primary goals of a given biobank and its internal guidelines.

Biobanks and biobank organization should therefore carefully monitor new developments with regard to regulatory (data) exclusivity.

3 Challenges in finding a balance between an open and a closed collaboration model

3.1 General

Large biomedical research projects depend on access to large amounts of HBM and data. That is why it is crucial to stimulate the exchange of HBM and data among the different members of the scientific community and biobanks. A number of challenges today still hinder access to large amount of HBM and data.

Although collections of HBM and data are considered fundamental research tools, we would argue that biobanks receive insufficient recognition for their investments and efforts. Little recognition is granted to purely technical contributions to research projects, such as the collection and provision of HBM and associated data. Guidelines of the International Committee of Medical Journal Editors and the Committee on Publications Ethics only grant authorship to research that participated in "drafting the article or revising it critically for important intellectual content" and "the final approval of the version

[104] REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance), OJ L 378/1, 27.12.2006.
[105] REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 1999 on orphan medicinal products, OJ L 18/1, 22. 1. 2000.

to be published" (ICMJE, 2009). The provision of HBM or data for a research project is not considered a sufficient ground to grant authorship. In some cases however, biobanks made important contributions to research projects via the collection, processing and organization of unique collections of HBM and data. We would argue that the biobank should be recognized for such contribution(106,112).

Biobanks could have an interest in becoming more than merely providers of HBM and data. When biobanks only supply HBM and data, they receive a one-time payment fee that most likely does not cover all costs invested by the biobank in the collection of HBM and data. If biobanks would participate in research projects, they could use the results of the research project to enrich their collections. They could contribute to the analysis and interpretation of research results. They could provide know how and expertise in relation to, for instance, the specific type of HBM and data that is required for a particular research project. Their expertise could be used to evaluate the statistical relevance of a certain amount of HBM and data to demonstrate a research hypothesis. Biobanks can create selections of HBM with specific characteristics for a research project and can collect additional HBM or data during the research project.

Biobanks, funding agencies, "open innovation" partnerships and journals increasingly require researchers to share the data and results of their research with other researchers. They are increasingly required to deposit them into publicly accessible repositories(115,146,147), such as dbSNP[106] in the US and the European Genome-phenome Archive ('EGA')[107]. This makes it possible to maximize the use of results of publicly funded research and to learn from and build on previous research. It reduces occurrences in which HBM and resources are spent on research projects that repeat existing research. Sufficient funding needs to be provided to guarantee the optimal storage and the security of the research results. Funding is also needed to be able to make the research results publicly available or share them with other researchers. Furthermore, biobanks, funding agencies and "open innovation" partnerships need to recognize the possibility to postpone the sharing of data during a reasonable period of time. They need to allow the initial researcher to publish the data or research results or to claim intellectual property rights in relation to such data or research results. The fact that one would claim intellectual property rights on research results does not preclude that the right holder could make the research results available under reasonable access conditions and fees.

Today biobanks often still depend on individual researchers or principal investigators for the collection of HBM and/or associated data. Empirical studies suggest that researchers are reluctant to share the HBM and data, which they collected(112,132). Some perhaps fear loosing control, once they transfer the HBM and data to the biobank. They made important investments – both in financial and human resources – in the collection, storage and processing of HBM and data and they perhaps feel that the collection of HBM and data might not exist without their contribution. The individual researchers may

[106] dbSNP collects discovered simple genetic polymorphisms and is maintained at the National Center for Biotechnology Information (NCBI), a division of the United States National Institutes of Health.
[107] The European Genome-phenome Archive (EGA) is a service for permanent archiving and sharing of all types of personally identifiable genetic and phenotypic data resulting from biomedical research projects.

have concerns regarding the possibility to continue their own research projects or to maintain the priority to publish research results(112) if they no longer can decide on the use of the HBM and data. That is why they could desire to be involved or consulted in the decision which future research projects can use "their" HBM and data(112). Funding agencies could require researchers to demonstrate that they will have access to the necessary HBM and data to be able to conduct the research project. This shows that access to HBM and data could also have an influence on the funding possibilities. Some have also argued that researcher acquire a certain academic reputation or prestige from the HBM and data which they collected(148). Finally collectors may worry about the confidentiality and security of the personal data of the donors(112). Some authors suggest developing additional and improved mechanism to share HBM and data between researchers and biobanks(132). Individual researchers would perhaps be more willing to share HBM and data, if they receive recognition for their contribution – for instance in the form of co-authorship – and a compensation of their investments.

3.2 Challenges specifically related to intellectual property rights on HBM

The comparative analysis of access arrangements – reported in Chapter 1 – revealed that the large majority of biobank initiatives do not have any policy in relation to upstream and downstream IPRs (83,149). Biobanks could hold upstream IPRs, such as *sui generis* database rights and/or copyrights in relation to their collection of HBM and data. Additionally, they could receive trade secret protection on their know how in relation to the collection, storage and processing of their HBM and data. Such IPRs could be a tool for the biobank to receive recognition for the important investments it made in the collection of HBM and data. It may be a way for them to recover some of its investments.

Some authors argued that biobanks should not be involved in downstream IPRs, i.e. IPRs on creations that accrue from the use of HBM and data in research projects. They argue that biobanks could only hold or participate in downstream IPRs, if the biobank made an intellectual or scientific contribution to the results of the research project. Today, this very often would not be the case(16). However, it has been argued above that biobanks could be entitled to a proper recognition for their "non-intellectual contributions" to research projects. Others argue that the participation of biobanks in downstream IPRs could hinder access to HBM and data because the biobank and the researchers would have to negotiate about the participation of both parties in downstream IPRs(134).

Even when a biobank decides not to be involved in downstream IPRs, this does not imply that it should not have any policy on such IPRs. Biobanks could make access to publicly funded collections of HBM and data conditional. They could include the obligation to allow the biobank or other researchers to use the downstream IPRs under reasonable access conditions and fees. Some authors have argued that such obligations could have a negative impact on the willingness to invest in research and the development of new applications(150). Researchers who use HBM and data to develop new health care applications made considerable investments to create such applications. They could be reluctant to make these applications available. They perhaps feel that the provision of HBM and data by the biobank does not justify a right to use such applications(134). Furthermore,

researchers use HBM, data and research tools from many different resources. Granting everyone the right to use the application would make its exploitation unnecessary complicate(150).

Biomedical researchers, clinicians and legal scholars debated many years on whether intellectual property rights should be granted on HBM or data derived from such HBM, such as stem cells, human genes, biomarkers or genetic diagnostics test (110,151,152). The discussion included the question under which conditions such IPRs should be allowed. Some argue that HBM, as such, is a product of nature that should be freely accessible to everybody and should not be the object of exclusive rights. The mere discovery of, for instance, a certain DNA sequence with interesting features does not constitute an intellectual contribution. Others argue that IPRs on HBM, such as patents, are essential for the survival of the biopharmaceutical industry. They defend that such IPRs would stimulate the development of products, therapies and tests based on HBM and derived data, such as diagnostic methods and therapeutics (110) (150,153,154). However, if the scope of protection offered by IPRs is too broad, IPRs could prevent or make it more difficult for others to develop new products, services or technologies, such as diagnostics test or research tools, cell lines or stem cells, …(112,148,150) (110). There also exists controversy about the excessive nature of IPR monopolies and/or restrictive licensing policies(155). A right holder could exercise its IPRs in such a way that it does not only claim exclusive rights in relation to the product, services or methods protected by its IPRs. The same right holder could extend his claims to other products, services or methods of which it may be doubtful if they are effectively protected under the concerned IPRs. Such use of IPRs creates a legal uncertainty as to whether certain products, services or test can be developed, produced or used without the permission of the right holder. A right holder can also require the fulfilment of unreasonable conditions or the payment of very high fees to allow the use of products or services protected by IPRs. A famous example in this respect is the Myriad Genetics case. Myriad Genetics developed a genetic diagnostic test to identify mutations associated with a significant risk of breast cancer and/or ovarian cancer in the BRCA1 (breast cancer 1, early onset) and BRCA2 (breast cancer 2, early onset) genes. Myriad obtained patent rights on two isolated human genes associated with breast and ovarian cancer (BRCA1 and BRCA2) and the genetic diagnostic testing methods. Those patents allowed Myriad to prevent other biopharmaceutical companies from developing similar diagnostic tests. It furthermore attempted to prevent European and US laboratories from developing and offering diagnostics tests that make use of the patented genetic sequences or methods, without Myriad's consent. Due to the exploitation policy of Myriad, the patents have been the object of a very strong debate(152,156,157) and have been attacked in legal proceedings. The US Supreme Court decided on 13 June 2013 that Myriad could not claim patent rights in relation to – merely – isolated fragments of BRCA-encoding genomic DNA. However, the Court did upheld Myriad's patents claims in relation to cDNA molecules encoding BRCA proteins(158). The mere isolation of DNA from the human body is thus not sufficient to obtain patent protection in the US(110), while in the European Union such isolation might lead – under certain conditions – to valid patent claims on DNA sequences(157).

Similar controversies arose around patents owned by universities, such as "*the University of Wisconsin's human embryonic stem cell patents, the Harvard and MIT's NF-kB pathway patent, the University of Rochester's patent on inhibition of the COX-2 pathway, and the Johns Hopkins*

University's purified stem cell patent" (155). The different cases resulted in a climate where both IPR agencies, funding organizations and right holders have become more aware of the possible negative consequence of claiming IPRs in relation to HBM and exercising those IPRs in excessive ways(132,155).

However, a number of empirical studies have shown that IPRs on HBM and data may not be the main factor inhibiting the sharing of HBM and data (112,132). Other important factors are competition between researchers, concerns about the commercialization of HBM and a lack of willingness among researchers to share HBM (see above).

Recital 26 of the EU Biotechnology Directive[108] stipulates: 'when a patent application is filed for an invention that is based on HBM or uses such HBM, the person whose body HBM was taken from, must have had the opportunity of expressing a free and informed consent thereto'. The lack of an informed consent does not, however, have a negative effect on the possibility to obtain a patent or on the validity of a patent(110). It is nevertheless advisable to take into account whether the consent of the donors or patients provides for the possibility to obtain IPRs on innovations or technologies developed with biobank material and data. The initial consent could specify that no IPRs can be obtained on the results of the use of HBM or data in a research project. If the consent does not stipulate anything in relation to IPRs, the question arises whether this automatically implies that one can obtain IPRs on the results of using such HBM and data. This question received quite a bit of attention when the direct-to-consumer genetic testing company 23andMe applied for a patent on a genetic test developed with data from users of the test. The consent form provided the possibility that 23andME could obtain intellectual property rights in relation to data collected in the framework of the genetic tests. Because 23andME only informed the users only after it had obtained the patent, many users of the test felt that their trust had been breached. Many authors have stressed how important it is that donors maintain trust in how their HBM and data is used in research. A loss of trust could results in fewer persons donating their HBM for research purposes, while biomedical research depends on such donations. It seems not enough for the informed consent to provide for the possibility to obtain IPRs on research results that accrue from HBM and/or associated data. It seems important to inform and consult donors in relation to the commercial use of HBM and data and the possibility of obtaining IPRs(155,159). The donors should be informed as to which policy would be applied to allow third parties to use the research results and IPRs(144). Such information and consultation should not only happen when the donor provides his HBM and data. It should also be applied in later stages, since one can often not predict from the start to which extent the use of HBM and/or data in research projects could lead to IPRs(129). Sarah Panis furthermore suggests that one could provide the possibility for the donor to claim a compensation of his damages, when IPRs were obtained in violation of the informed consent(110).

[108] DIRECTIVE 98/44/EC of the EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 July 1998 on the legal protection of biotechnological inventions, *Official Journal L 213, 30/07/1998 P. 0013 - 0021*

4 Potential strategies and options to stimulate the sharing of HBM, data and research results

This chapter will discuss potential strategies and options to create a right balance between several facets that are essential for the creation of research tools and medicinal products and therapies. These include facilitating access to HBM and data, promoting scientific openness and incentivizing sufficient investments in life sciences (150,160).

It is important to recognize and protect the interest of the different stakeholders that contributed to the collection of HBM and data, such as donors, funders and institutions that establish and manage biobanks. However, one should stimulate researchers to use HBM and data and share the results of their research as much possible. It is important to take into account their legitimate interests in valorising their research results.

We will discuss a number of possible strategies and options, such as (1) the development of a biobank policy on the involvement in downstream and upstream IPRs; (2) the development of biobank policies on upstream IPRs held by researchers on research results accruing from use of HBM and data from publicly funded biobank; (3) stimulating the sharing of research results; (4) increasing funding for maintaining operating collections of HBM; (5) review mechanism to recognize contribution of biobanks and collectors to research projects and (6) involve all stakeholders in policies on commercialization, IPRs and sharing of non-financial benefits.

4.1 Possible solutions related to IPRs

4.1.1 Policy on involvement of biobanks in downstream and upstream IPRs

There have been a number of examples where IPRs were used in an excessive way that inhibited the development of new biomedical products, therapies or tests. This lead to controversy on IPRs on HBM and data. However, the mere fact of obtaining IPRs does not automatically imply that such rights will be exercised in an excessive way(129).

Literature contains several examples in which publicly funded institutions exercised IPRs in such a manner that stimulated biomedical research and did not hinder access to the scientific advancements of such research. Stanford University met with potential users to discuss how it could under reasonable conditions provide access to production methods for recombinant DNA protected by patent rights. It also decided not to attempt to obtain an extension of those patents right. Stanford University filed a terminal disclaimer, which meant that all subsequent divisional applications claiming recombinant DNA would expire on the same data as the original patent(161).

The Association of American Medical Colleges and a number of top universities in the US released policy recommendations to promote access to genetic diagnostic technologies(162). The Massachusetts General Hospital determined its patenting and licensing strategy in relation to research into Huntington's disease in consultation with the Huntington Disease Consortium(155).

A number of reasons could justify the fact that biobanks would become involved in IPR policies. An IPR policy could constitute a tool to enhance the acknowledgement and protection of the interests of the biobank. It could stimulate the development of biobanks as essential research tools or infrastructures(150). It could also provide an additional tool to recover some of the investments of the biobank. Furthermore, it may strengthen the bargaining power of biobanks to request applicants to feed some of the scientific advancements and benefits back into the biobank and the health care system and to share their research results with the scientific community.

In order to ensure that biobanks maintain public trust and support, it is advisable that a number of elements are taken into account in the development of IPR policies. First, biobanks should consult and inform stakeholders about their approach and policies in relation to IPRs.

Second, biobanks should be careful not to exercise their IPRs in an excessive manner.

IPRs in relation to the database and the software developed in the framework of the biobank should not be used to limit access to the collection of HBM and data. It could however allow biobanks to control that only those applicants that comply with reasonable and non-discriminatory license conditions use their databases and software. It could be used to prevent others from copying their databases, technology, and software. Biobanks could also, under reasonable conditions, request applicants to allow access to data generated with creations protected by IPRs of the biobank (150,155).

Trademarks could allow biobanks to protect their name and logo. This would allow biobanks to prevent others from using the same or similar names for ‘products’ or ‘services’ that are not provided by the biobank and that could damage the reputation of the biobank and its ‘products’ and ‘services’.

The main aim of an IPR policy should not be to generate profit(155). One could, however, charge reasonable user fees for the use of the database and/or technology within a biobank. Different users fees could be applied depending on whether the database and/or technology are used for commercial and non-commercial purposes.

The policy should contain clear information on which IPRs the biobank could claim in relation to the collection of HBM and data and which rights the potential users can hold in relation to his research results.

Unless the biobanks made an important (intellectual or scientific) contribution to the results of a research project, biobanks could decide to focus on the protection of their upstream IPRs and not on so-called downstream IPRs. Researchers could be hesitant to use HBM and data from a biobank that would claim downstream IPRs in an excessive manner.

Discussions about the desirability of exclusive rights on HBM, as such, could be avoided if biobanks would commit themselves to not claim IPRs in relation to basic HBM and basic data and data directly derived from such HBM. They could limit their IPRs to their real contributions or added value to collections of HBM and data(160). Such added value could consist of the investment made in creating high quality databases and software and the knowhow and trade secrets in relation to the optimal manner of collecting, storing and processing HBM and data.

4.1.2 Policy on downstream IPRs held by researchers on research results accruing from use of HBM and data from publicly funded biobank

A proper policy on downstream IPRs should encourage applicants not to obtain excessive IPRs, but should at the same time contain sufficient incentives to innovate(145,150,163).

The desirability to obtain IPRs is considered in a different way depending on whether the IPRs would relate to (a) basic upstream data directly derived from the biobank, (b) basic research tools or enabling technologies and (c) downstream clinical applications with potential commercial value at the other end.

The biobank policy should prohibit users from strategically obtaining IPRs on primary HBM and data or upstream data (directly) derived from the collection of HBM and data. For such IPRs could limit the possibilities of other applicants to use such HBM and data for commercial purposes(163).

The scientific community should be able to access and use basic research tools and enabling technologies under reasonable and non-discriminatory access conditions. That is why some authors suggests that applicants should be encouraged to grant a non-exclusive license to use such research tools or enabling technologies to the users of the biobank. In the same line of thinking, the applicants could grant the biobank a non-exclusive right to sublicense the tools or technologies to its users. The scope of such license could be limited to (a) use in research projects; (b) use by academic institutions; or (c) use for internal purpose only. It could explicitly exclude the possibility that a third party would valorise or commercialize the concerned research tools. Some suggest that such “so-called grant back arrangement” works best for research results that are sufficient upstream, such as genetic sequence databases, cell lines and assays(146,150).

In order to stimulate biomedical innovation, applicant should be given the freedom to obtain exclusive IPRs. They should be allowed to commercialize downstream clinical applications or products, such as diagnostic tests, therapies and medicines that arise from using the biobank(146,150,163).

The biobank could however maintain the right to request a non-exclusive license on the IPRs that cover the basic materials. This could avert that applicant would use the IPRs in such a manner that would limit access to and use of the collection of HBM and data.

Literature contains a number of examples that could inspire biobank policies on downstream IPRs. Researchers that wanted to use data from the International Hap Map Consortium had to comply with a click- and wrap-license that aimed to ensure that the data generated by the Project would remain available to all users. Under the Hap Map license, applicants were free to use the data for any type of analysis and to publish the results of those analyses. Applicants were, however, not allowed to include details of individual genotypes that the HapMap Project had not yet released in publications. They furthermore had to commit themselves not to file any patent application that contained claims to any composition of matter or any use of SNP, genotype or haplotype data (directly or indirectly) obtained from the Genotype Database. Exception was made under condition that such claims did not restrict the ability of others to use at no cost the Genotype Database or the data it contains for other purposes(164). Licensees were entitled to obtain patents on new or inventive associations between SNP or haplotype and a particular disease risk or drug response, if such patents would not limit

access to the underlying HapMap Data(145). The license also provided that applicants could only transfer HapMap Data to third parties that were bound by the license. Unfortunately it appeared that researchers had problems to convince scientific journals to publish research data under the conditions stipulated in the HapMap License(150).

Navigenics, a consumer genomics company, commits itself to grant non-exclusive, non-discriminatory licenses on its patents in relation to the association between a SNP and the susceptibility for a particular disease(145). The Malaria Genomic Epidemiology Network allows participants to obtain IPR protection for clinical applications if 3 conditions are met: *(a) the discovery must be directly relevant to a medical application; (b) it must be licensed for development immediately; (c) the discovery must have been shown to require IPR as a stimulus for further development."* If possible such IPRs should be licensed to non-profit organizations(165).

The UK Biobank Access Procedures(166) contain specific IPRs provisions that 'aim to make the collection of HBM and data available to all approved researchers, but at the same time facilitate development of clinical advancements'. The IPR provisions contain a division of rights between the UK biobank and applicants in relation to (1) the database of HBM and data; (2) researcher's generated datasets and (3) inventions and associated IPRs. First, the IPR provisions provide that the UK Biobank is the owner of the database and the HBM and holds database rights and copyright in relation to data stored in biobank. The applicant is granted a limited non-exclusive license to use the data and HBM in the framework of an approved research project and for limited period of time. Second, applicants or their institutions hold IPRs on researcher-generated datasets. The UK Biobank is granted a non-exclusive, royalty free license to use the datasets and make them available to other approved researchers, i.e. researchers that are granted access to the UK Biobank. Finally the IPRs provisions stipulate that the UK Biobank makes no claims on inventions and associated IPRs developed in the framework of the research project. In the occurrence that IPRs are used to unreasonably restrict biomedical research or health care, the UK Biobank would be granted a non-exclusive and royalty free license. This license would give them the right to use and allow other approved researchers to use the concerned inventions and IPRs in their research projects. Finally, the IPR provisions clarify that it would not expect an applicant to obtain IPRs on naturally occurring genetic sequences, biomarkers, proteins and biochemical processes.

The P3G generic access agreement for population genomic studies (2011) stipulates that applicants should not claim IPRs on HBM and data derived directly from a population genomic study. Applicants are allowed to obtain patents on downstream inventions, if they agree to implement licensing policies that will not obstruct further research. Finally the Applicants own all results, data and inventions which arise from their research project, but they are expected to grant "*a perpetual, non-cancellable, royalty-free, worldwide license, with right to sublicense, to use study results for all purposes"* to the population genomic study(77).

4.2 General solutions

4.2.1 Stimulating the sharing of research results

Biomedical research could benefit in different ways if biobanks would require applicants to share the upstream results and data that accrue from research projects with them. Sharing both positive and negative results of research projects would allow other researchers to learn from previous projects and build on existing knowledge. When making research results publicly available, one would have to demonstrate that the invention is novel and/or inventive compared to the publicly available data. So this would also limit the danger of obtaining IPRs on HBM and data directly derived from the collection of HBM and data and upstream research results. Returning data about the biological characteristics of the HBM to the biobank could also enrich the collection of HBM and data. Additional information on the collection of HBM and data could be useful for future research projects that use the collection. The information could be used to improve the quality of the collection of HBM and data.

Researchers would only accept to share their research results if a number of conditions are fulfilled. The necessary infrastructure needs to be available to store and allow access to the research results. Appropriate mechanism should be created to ensure that research results are only used for research projects that obtained the necessary ethical and/or scientific approval(146). The researchers that generated the data, need to be given sufficient time to analyse and publish their research results and to obtain IPRs in relation to the research results(145,146,163). It would be advisable that data generators would be informed and possibly also consulted, when a new researcher applies for access to research results. Finally, upfront rules should be stipulated on the conditions that apply to determine whether the data generator is entitled to receive a recognition and/or compensation for his contribution to the new research project. Depending on how important the contribution of the initial researcher is the conditions could provide for an acknowledgement, co-authorship or even participation in IPRs that accrue from the new project(167).

4.2.2 Review mechanism to recognize the contribution of biobanks and collectors to research projects

Organizations and persons that provide HBM and data for research projects are often only mentioned in the acknowledgement. Such acknowledgement could increase the visibility of the biobank, but only has a limited impact.

Guidelines on authorship provided by ICMJE and other organizations focus on intellectual contributions to publications. They value other types of contributions to research projects to a lesser extend. Unless they demonstrate that they participated in the drafting or the revision of the publication, persons or institutions that contributed to the collection, processing and analysis of HBM and data are in principle not eligible for co-authorship.

This is unfortunate, since co-authorship of publications could constitute an important incentive to participate and contribute in research projects. An empirical study from FM Colledge, BS Elger and DM Shaw revealed that biomedical researchers in Switzerland unanimously agreed "*that authorship is a motivation to make samples available to other researchers, or collaborate with individuals external to*

their own department in some way (168).*"* It is therefore not surprising that research project sometimes ignore formal guidelines on co-authorship to acknowledge persons that made important contributions that would not fulfil the general applicable criteria on co-authorship(168).

Considering the above, we suggest revising international guidelines on co-authorship. It should be clarified which type of contributions could result in co-authorship. It would raise awareness and appreciation with regard to the more essential technical or scientific contributions, such as the development of unique databases of HBM and data. This could prevent that international guidelines are increasingly ignored and that uncertainty would arise on the rules that would be applied to grant co-authorship to participants in biomedical research projects(168).

An alternative could be that biobank policies would clarify how contributions to research projects would be recognized and rewarded(16). One could for instance distinguish the following types of contributions: (1) the mere collection, storage and provision of HBM and data; (2) the systematic collection, storage and provision of HBM and data according to certain (selection) criteria; (3) hypothesis-generated data and collected HBM (possibly in the framework of a previous research project); and (4) the analysis and interpretation of data. A similar approach is suggested in the International Charter of principles for sharing bio-specimens and data(106).

Another mechanism that is currently developed to acknowledge the contribution of HBM and data to research projects and to increase the visibility of biobanks is the Bio-Resource Impact Factor (BRIF). BRIF aims to calculate the impact of collections of HBM and data on biomedical research. It is modelled in analogy to existing impact factors systems for publications in journals. BRIF would provide objective data on the "*1. the quantitative use of a collection of HBM and data, 2. the quality and importance of research results involving it, and 3. the scientific and management efforts of those who set up and made available a valid bioresource and their institution"*[109]*.*

4.2.3 Involve all stakeholders in policy on IPRs

IPR policies will receive more support when biobanks carefully consider and address the concerns of the different stakeholders in relation to the possibility of obtaining IPRs on HBM and data(155).

Biobanks need to be transparent to donors about the decision to claim IPRs on collections of HBM and data. They should explain that such IPRs will not relate to the HBM and data as such, but only to the added value created via operations conducted on the HBM and data. Donors need to be clearly informed about the fact that their HBM and data could be used for research projects that could result in commercial applications.

A clear, upfront policy should be developed and communicated to the different stakeholders about the conditions that apply to determine whether applicants can obtain IPRs on the results of their research project.

[109] *http://www.p3g.org/brif-bioshare-pilot-study*

It would be advisable that biobanks create a continuous dialogue with the donors, the applicants and funders on how they implement and update their IPR policy. Omitting to consult stakeholders on the IPRs policy could lead to a lack of support. Researchers may be more motivated to collaborate and share research results with the biobank, when a clear IPR policy has been developed.

Finally biobanks could consider developing a policy on the sharing of non-financial benefits that arise from using HBM and data in research projects between the biobank, the applicants and the donors. Such policy could provide that part of the benefits should be fed back in to the collection of HBM and data or other research or health care infrastructure. Applicants could commit themselves to make the results of the research project publicly available. Simultaneously or alternatively they could allow – under reasonable conditions and fees – access to applications developed in the framework of the research project, such as genetic test or therapeutics.

5 Conclusions

This chapter provide more in-depth information on the possibility and desirability of obtaining IPRs in the context of publicly funded collections of HBM and data.

An IPR policy may be used as a tool to enhance the acknowledgement and protection of the interests of the biobank and to stimulate the development of biobanks as essential research tools or infrastructures(150). One should however avoid ending up in a situation in which IPRs would constitute an obstacle to the use of HBM and data in research projects.

IPR policies should contain clear information on which IPRs the biobank might claim in relation to the collection of HBM and data. It should also be clear which IPRs the potential users can hold in relation to his research results. Unless the biobank made an important (intellectual or scientific) contribution to the results of a research project, it could be useful for them to focus on the protection of their upstream IPRs and not on downstream IPRs. A proper policy on downstream IPRs should encourage applicants/researchers not to obtain excessive IPRs. The policy should however contain sufficient incentives to innovate. Substantial and risky investments are made to develop downstream clinical applications or products, such as biomedical treatments or diagnostics. Applicants have a legitimate interest to obtain IPRs on downstream clinical applications or products (134). Basic upstream data, research tools and enabling technologies should, however, remain available to the scientific community(145,150,163). Finally we suggest revising international guidelines on co-authorship to clarify which type of contributions could result in co-authorship. Such new guidelines could focus their recognition on the more essential technical or scientific contributions to research projects and less on the participation in drafting the final manuscript (168). Alternatively biobank policies could clarify how contributions to research projects would be recognized and rewarded(16,106,119).

Part 4: General discussion

The PhD project studied the legal framework that determines the relationship between a biobank and a researcher who applies for access to HBM and data stored in a biobank. The legal framework is regulated by the applicable legislation. It is also to a large extent determined by access arrangements. Such access arrangements consist of guidelines, best practices and opinions from biobank organizations. They furthermore consist of policies and agreements adopted by biobank networks and biobanks that define the rules on access to and use of collections of HBM and data.

1 General discussion of the research findings

A specific discussion of the results concludes each chapter. Therefore we will present a general overview of the findings in this part.

1.1 Harmonization across biobank initiatives

The comparative analysis of access arrangements revealed a lack of harmonization on how access conditions are defined and implemented (see conclusion of Chapter 1). This lack of harmonization can be explained by the fact that the concepts of 'biobanks' and 'biobank networks' represent a heterogeneous group of infrastructures that collect various types of HBM and data (as explained in the General Introduction). Some discrepancies could also be explained by the various approaches on ethical and legal issues in biobanking in the different countries (23). This heterogeneity in access conditions makes it questionably whether one should provide 'one size fits all' conditions on access to biobanks(1). Attempts to harmonise access conditions could focus on particular types of biobanks, such as tumour or stem cell banks or population-based biobanks. In another approach they could focus on rather technical issues, such as quality standards or minimum data sets. Harmonization could also focus on specific access conditions, such as IPRs, the sharing of research results(169) and non-financial benefit sharing. The interviews (Chapter 2) and the legal study (Chapter 3) confirmed that also such specific conditions are not yet harmonized. Finally, attention could be given to some other biobank initiatives (such as OECD and P^3G), which did not attempt to harmonize access rules, but rather to develop best practices or guidelines. Such best practices (3,36,77,163,170) or guidelines do not suggest a uniform set of rules. They aim to provide a general (legal) framework that can be used as inspiration for the creation of access rules within other biobank initiatives. In this way they may indirectly stimulate harmonisation.

A considerable number of access arrangements – studied in Chapter 1 – did not contain clear information on how the biobank initiatives (should) implement several of the studied access conditions. The lack of clear information on access conditions could hinder access to biobanks and biobank networks(14,16,63,69,77,81,82,84,91). Applicants need to be informed on the rules that need to be respected to obtain access to collections of HBM and data.

Historically many clinicians and researchers created their own collections of HBM and data. The analysis in Chapter 1 revealed a trend to grant custodianship to biobanks or biobank networks and no longer to individual collectors or principal investigators (see section 4.3 of Chapter 1). The interviews in Chapter 2 confirmed this trend. Since the last decennium many institutions centralize the HBM and data collections from different departments in one single biobank infrastructure. This can be explained

by the fact that biomedical research requires access to large amounts of HBM and data of high quality(23,65,81,91).

The majority of access arrangements provides custodianship of HBM at the level of a biobank and not at the level of a biobank network (see section 4.4 of Chapter 1). This is probably due to the fact that biobanks want to maintain control over the HBM that they collected.

Finally the comparative analysis in Chapter 1 confirmed that the majority of the biobank initiatives establishes an access committee to evaluate requests for access to HBM and data (see section 4.6 of Chapter 1). The mandate of such access committees is not always clearly defined. Chapter 2 dug deeper into the question how biobanks define such mandate.

1.2 Custodianship on HBM and data stored in biobanks

The interviews (Chapter 2) aimed to gain a more in-depth understanding on how access arrangements (as explored in Chapter 1) are applied in the daily practice of biobank initiatives. The first part of the interview focused on the evaluation of access requests by access committees (see section 3.1 and 4.1 of Chapter 2). REC (Research Ethics Committee), access committees and possibly also funding bodies evaluate research projects from applicants that request access to collections of HBM and data. The interviews raised the importance of clarifying the interaction between those different entities (105). There was no consensus among the interviewees on whether and to which extent access committees of biobanks should evaluate the quality, the scientific and medical usefulness and the ethical value of research projects. The legal study in Chapter 3 revealed that the existing legislation does not contain any guidance in this respect. The interviewees did agree that access committees should only evaluate access requests on the condition that they dispose of sufficient expertise, experience and independence(11,23,105,106). Two interviewees with a legal background posed the question whether some or all of the evaluation criteria should be determined by binding legislation. They furthermore highlighted that the criteria should be equitable and proportionate. The legal study in Chapter 3 revealed that the Best Practice 7.4 of the OECD Guidelines for Human Biobanks and Genetic Research Databases stipulates in this respect that custodians “need ensure that any stratified access or fees policies are fair, transparent and do no inhibit research”(36). There was a consensus among the interviewees that equal access conditions should apply to internal and external academic applicants and non-academic applicants (see section 3.3 of Chapter 2).

The informants in Chapter 2 seem to agree that the custodian of the biobank has the right to take the final decision on whether leftover HBM should be returned or destroyed. However, the interviews demonstrated the difficulty to determine generally applicable criteria on whether the biobank should request the return or destruction of leftover HBM (see section 3.2 and 4.2 of Chapter 2). An important criterion (according to the interviewees) is whether one can guarantee the quality of the leftover HBM for future research purposes. The comparative analysis (Chapter 1) and other previous studies confirmed that biobanks apply different policies on leftover HBM (17,67). Following the interviews, there is however no doubt that applicants need to obtain an approval of the (access committee of a) biobank – and a research ethics committee – to use leftover HBM in another project. There was

furthermore a consensus that applicant should not transfer leftover HBM to third parties without the prior authorization of the custodian of the biobank.

The access fees charged by biobanks are often insufficient to compensate all costs in relation to the collection, storage and distribution of HBM and data for research purposes. New mechanisms need to be developed to feed some of the benefits of biomedical research back into the biobank infrastructure and the health care system(23,111). The interviewees were rather sceptical about the idea that providers of HBM and associated data should be able to participate in downstream IPRs or royalties on such IPRs (see section 3.3 and 4.3 of Chapter 2). Chapter 4 on IPRs and biobanking confirmed that biobanks should only be involved in downstream IPRs if they made a (intellectual or scientific/technical) contribution to the results of a research project. The interviews in Chapter 2 (section 3.3 and 4.3) suggest that public biobanks might charge a higher access fee to industrial applicants – compared to academic applicants – for the access to a publicly funded collection of HBM and data(16,25). This could be justified by the fact that those collections have been created with public funding. The comparative analysis in Chapter 1 had already shown that several biobank initiatives apply different access fees depending on the type of applicant. However, the best practice 7.4 of the OECD Guidelines stipulates that the custodian of a biobank has to ensure that any stratified access conditions and fees are fair, transparent and do not inhibit research (see section 3.1.3 of Chapter 3).

There was consensus among the interviewees that an applicant could be required to share his research results with the biobank and/or other researchers (section 3.4. and 3.5 of Chapter 2). This is no surprise, since the majority of the access arrangements studied in Chapter 1 provided that a biobank could require the return and/or the sharing of research results. One should however protect the legitimate interests of the researcher that generated the research results. The OECD Guidelines for Human Biobanks and Genetic Research Databases (studied in Chapter 3) suggest in this respect that a biobank should develop a policy on whether and how the results of research and analyses carried out using HBM and data stored in biobanks should be returned to the biobank. Chapter 4 studies more in depth how biobanks could develop policies on the return and sharing of research results.

None of the interviewees was in favour of the idea of granting applicants the exclusive right to access and use a specific collection of HBM and data. Such exclusivity is looked upon as an unjustified limitation to the accessibility of HBM and data for other research projects (see section 3.6). This explains why only a small minority of access arrangements (studied in Chapter 1) stipulates some kind of exclusivity.

Today, quite some collections of HBM and data are established at the initiative of the principal investigators of specific research projects. Furthermore biobanks still rely on individual clinicians or researchers for the collection of specific HBM and data. Biobank initiatives could recognize such contribution by granting a temporary priority right to conduct research with the collected HBM and data and to allow publication of the results(16,106).

1.3 Legal framework governing access and use of HBM and data for research purposes

The legal study in Chapter 3 showed that the Belgian legislation applicable to biobanks mainly focuses on the rights and obligations of the donor and the custodian. Fewer provisions relate to the rights and obligations of the applicants. The legal framework contains, for instance, quite detailed rules on the obligation to respect the informed consent of the donor and the protection of the personal data of the donor. The study of legal documents (Chapter 3) also revealed a considerable list of rights and obligations held by the custodian of a biobank. Finally several legal documents stipulate that a REC or another competent authority should review the aims and activities of a biobank.

The Belgian and Danish legislation applicable to biobanks contain specific rules on the review of access requests by ethics committees (see Chapter 3). It does not provide anything in relation to the mandate of an access committee. Some international normative instruments do provide additional guidance on the role of an access committee and the development of access policies, procedures and mechanisms (see section 3.1.3 of Chapter 3). The OECD Guidelines for Human Biobanks and Genetic Research Databases (36) formulate a general principle on the development of biobanks policies. They express the principle that biobanks should develop policies on the commercialization of HBM and data, IPRs, the sharing in scientific advancements and its benefits and the sharing of research results. They do not contain concrete guidance on how to develop such policies. The interviews in Chapter 2 (sections 3.3 and 4.3) revealed that no consensus exists among biobank initiatives on how to develop a policy on IPRs and benefit sharing. Chapter 4 studied how biobanks could develop policies on IPRs, the sharing in scientific advancements and its benefits and the sharing of research results.

1.4 IPRS in biobanking: challenges and opportunities for translational research

Chapter 4 of this PhD studied the possibility and desirability of obtaining IPRs in the context of publicly funded collections of HBM and data. Both the comparative analysis of access arrangements (Chapter 1) and the interviews (Chapter 2) confirm that the majority of the biobank initiatives did not develop any policy in relation to IPRs. This might be explained by the fact that the existence and especially the exercise of IPRs in relation to HBM and data have been found controversial in the past. The exclusive nature of IPRs could also be considered incompatible with the need to facilitate access to biobanks(131). An IPR policy may just as well be used as a tool to enhance the acknowledgement and protection of the interests of the biobank and to stimulate the development of biobanks as essential research tools or infrastructures(150). One should however avoid ending up in a situation in which IPRs would constitute an obstacle to the use of HBM and data in research projects. Chapter 4 highlights the main challenges and suggests possible strategies and options with regard to this topic. It tackles the question of how to address and manage IPRs directed to HBM, the associated data stored in the biobank and the results of research using the HBM and associated data. We looked amongst others into the question whether biobanks should be involved in upstream and downstream IPRs. Finally the chapter highlights how biobanks could be involved in the development of policies on the sharing of research results. We also suggest developing policies to ensure an increased recognition of the contributions of biobanks and collectors to research projects.

1.5 Does the existing legal framework regulate the key access conditions?

The PhD project studied to which extent the existing legal framework regulates the different key access conditions identified in the empirical studies (Chapter 1 and 2) and the legal study (Chapter 3). This allows us to determine to which extent certain access conditions need to be addressed via additional legislation or soft law or access arrangements.

Chapter 1 revealed that several "key access conditions" are regulated by the majority of the studied access arrangements, such as (1) the level of custodianship; (2) the establishment of access committees; and (3) the mandate of such access committees.

We concluded from Chapter 2 that a number of "key access conditions" would preferably be regulated via access arrangements, such as (1) the access conditions and fees that apply to industrial and external applicants; (2) priority setting; (3) priority access for collectors of HBM and data; and (4) the return and destruction of leftover HBM.

Chapter 3 revealed that other "key access conditions" are mainly regulated via legislation or soft law, in particular: (1) the review of the aims, activities and policies of biobanks by RECs; (2) the rights and obligations of custodians; (3) the review of access requests by REC; (4) the principle that one should not generate profit on HBM (as such); (5) data protection; (6) consent.

A limited number of 'key access conditions" seem to be insufficiently regulated via the existing legal framework, in particular: (1) the sharing or returning of research results; (2) benefit sharing; and (3) intellectual property.

2 Recommendations to facilitate access to biobanks

2.1 An optimal legal framework combines legislation, soft law and access arrangements

The PhD project studied the question whether the existing legal framework is adapted to the needs of the different stakeholders concerned by access to biobanks. It engages in the question as to which extent legislation or soft law is required for the creation of a transparent, feasible and encouraging legal framework for access to biobanks. Many different players and instruments determine the legal conditions for access to biobanks. National legislation, international normative instruments and access arrangements each play a distinct role in the regulation of access to biobanks. Access arrangements do not need to contain specific rules on legal issues that are already sufficiently regulated by national legislation or international normative instruments (or soft law). The protection of personal data is a good example of an issue that access arrangements do not have to deal with in detail given the well-developed international, European and national legislation in this regard. Another issue that is regulated in detail by legislation and soft law is the requirement to obtain the informed consent of the donor for the removal, the storage and/or the use of HBM and data for research purposes. On the other hand, the existing legislation and soft law does not provide any guidance on how to calculate financial and material compensations for operations conducted with HBM and data. Here, guidance in access arrangements could provide an additional tool to avoid the commercialization of HBM.

Taking into account the international embedment and heterogeneous nature of biobanks, legislation should not over-regulate access to biobanks. That is why we doubt, for instance, whether national legislation or international normative documents should regulate the requirement to return or destroy leftover HBM. The interviews (Chapter 2) demonstrated that no general rules could be formulated in this respect. One could also doubt whether the evaluation of access requests by access committees should be regulated in detail by national legislation or international normative instruments.

Some aspects of access to biobanks could be regulated via codes of conduct, guidelines and best practices. Those instruments could, for instance, be used to develop policies on (1) priority access of collectors of HBM and data; (2) the sharing or returning of research results; (3) benefit sharing; and (4) intellectual property. The advantage of such instruments is that they are created after consultation with the different stakeholders involved in biobanking. Such instruments may also be more easily adaptable in order to take new evolutions into account. Although they are not enforceable as national legislation, they do have an important influence. An example of this is the Code of Conduct developed in the Netherlands by FEDERA – the Dutch Federation of Medical Scientific Societies – and COREON – the Commission on Regulation in Research –. It was realized in close collaboration with the Dutch Patient Consumer Federation, the Federation of Parent and Patient Organisations and BBMRI-NL. This Code of Conduct contains relatively detailed rules and principles on how to deal in a responsible manner with HBM (and data) in the context of health research(171). The Code of Conduct created a certain extent of harmonization, since many biobanks, biobank networks and organizations in the Netherlands committed to respect this common set of rules and principles. Other important access arrangements have been developed by the National Cancer Institute in the US(3), ISBER(85), the OECD(36,170) and P^3G(77,163).

2.2 Biobanks should develop clear policies on the evaluation of access requests

Biobanks should provide publicly available information about their access arrangements and procedures(36,172). Access arrangements should clarify the mandate of access committees. They should in particular specify which criteria and procedures will be applied in the evaluation of access requests (11,16,36,105). The procedure for the evaluation of access requests should protect the interests of the donor and the biobank. It should, for instance, avoid that HBM and data is wasted on research projects of insufficient quality. It should not, however, become unnecessarily burdensome. For instance, an access committee should not evaluate the same criteria as a REC and/or a data protection authority. Access arrangements could clarify how access committees will supplement the mandatory evaluations by REC or other competent authorities(6).

When an access committee evaluates access requests and the scientific merits of applicants, it needs to make sure that it disposes of the necessary competence to make such evaluation. That is why it may be advisable to consult external reviewers in the evaluation of certain access requests.

Access arrangements should contain clear instructions on which information an applicant needs to provide in his research protocol(36). One could refer in this respect to the Good Clinical Practices that are applied in clinical trials. They could constitute a source of inspiration.

Access arrangements should stipulate to which extent certain types of research will be given priority(36). One could for instance imagine that diseases-oriented biobanks would prioritize research that corresponds with their own core field of interest.

Access arrangements should clearly specify the rights and obligations of the custodian, the applicant and the donor in relation to the collection of HBM and data.

Finally one should avoid 'restrictive' access arrangements that would limit access to collections of HBM and data and as consequence would unnecessarily hamper the development of biomedical research.

2.3 Define the conditions for access by industrial companies

The majority of the biobank initiatives agree that industrial companies – such as pharmaceutical and biotechnological companies – can access and use HBM and data from publicly funded biobanks. Industrial companies play an important role in the transformation of research into a drug candidate and eventually into a medical product. However, access by industrial companies should not have a negative impact on the donors' trust and willingness to provide HBM and data to biobanks(129). That is why biobank initiatives should clearly communicate about their relationships with industrial companies. It would be desirable to clearly define the conditions under which industrial companies can access publicly funded collections of HBM and data. Those conditions could be developed in consultation with the different stakeholders, such as the funders of the biobanks, the donors and the applicants.

2.4 Recognize the contribution of individual collectors

The comparative analysis of access arrangements and the interviews confirmed that custodianship over HBM and data has shifted over time from individual collectors to biobanks. However, individual collectors still make important contributions to the collections of HBM and associated data. Individual collectors could also provide important know how on the HBM and associated data. Proper incentives should be given to the individual collectors and their contributions (6). It could be envisioned to grant certain collectors a temporary priority right to conduct research with the collected HBM and data and to publish the results(16,106). It is considered good practice to inform the collectors of HBM and data, when such HBM and data is used in research projects. One should however investigate the practical implications of such practice. It may be a good idea to also consult individual collectors in the decision to make HBM and data available for a specific research project. This does not imply a veto right for the individual collector. The final decision to distribute HBM and associated data remains with the custodian of the biobank.

2.5 Develop policy on sharing of research results

Previous studies confirmed that an increasing number of biobanks(67) and funding bodies(115) require researchers to make their research results publicly available. Such requirement is motivated by the desire to maximize the use of results of publicly funded research(113,116). Some authors also invoke the principle of reciprocity. Researchers could be expected to share their results with stakeholders that contributed to the collection of HBM and data, such as biobanks and

donors(106,108). However, the sharing of research results will only be useful and acceptable for researchers if the following three conditions are fulfilled. First, the proper infrastructure needs to be available to store and allow other researchers access to the research results (116). Second, the conditions under which other researchers can access the results should be clearly defined. Finally, it should be taken into account that researchers could have a legitimate interest to request that some research results remain confidential. This is necessary to allow the researchers to publish their results and possible obtain IPRs on clinical applications based on those results(105,106,108,116,119).

2.6 Develop policy on intellectual property rights

IPR policies could constitute an important tool to protect the considerable investments made in the creation of collections of HBM and data. Such policies will only be successful if the interest and concerns of the different stakeholders are taken into account(155). Transparency towards the donors is important. The donors should be aware of the possibility of obtaining and exercising IPRs in relation to the collection of HBM and data. The policy should contain clear information on which IPRs the biobank (or the collecting researchers) might claim in relation to the collection of HBM and data. It should also be clear which IPRs the potential users can hold in relation to research results obtained from using HBM and data. Unless the biobank made an important (intellectual or scientific) contribution to the results of a research project, it could be useful for them to focus on the protection of their upstream IPRs and not on downstream IPRs. A proper policy on downstream IPRs should encourage applicants/researchers but also biobanks not to obtain excessive IPRs. The policy should however contain sufficient incentives to innovate. Applicants have a legitimate interest to obtain IPRs on downstream clinical applications or products (134). Basic upstream data, research tools and enabling technologies should, however, remain available to the scientific community(145,150,163). Finally we suggest revising international guidelines on co-authorship to clarify which type of contributions could result in co-authorship. Such new guidelines could recognize more essential technical or scientific contributions to research projects (168). Alternatively biobank policies could clarify how contributions to research projects would be recognized and rewarded(16,106,119).

2.7 Involve donors and patients in the biobank policy

The future evolution of biobanks depends to a large extent on the willingness of donors to provide HBM and data for biomedical research. That is why biobanks need to make sure that they maintain the trust of those donors. The interests and concerns of donors and patients should be taken into account in every aspect of a biobank policy(129). Biobanks should maintain an open dialogue with the donors about the activities and the policies of the biobank. Finally it is important to create more public awareness of the important contributions of biobanks to biomedical research and innovation (6).

3 Methodological considerations

This PhD project focused on access to biobanks. It focused, more precisely on the relationship between the custodian of a biobank and the applicant/researcher who requests access to HBM and data stored in the biobank. We paid less attention to both the – no doubt important – relationship between the custodian and the donor and to the relationship between the donor and the applicant. We made this choice in order for our study to complete existing studies which focused on public perception and participation in biobanks, governance, consent, and return of incidental findings (23,56–59,61–68). However, some studies of this PhD project did touch upon the mentioned relationships. In the framework of the qualitative study reported in Chapter 2, we interviewed, for instance, four patient representatives. In addition, the comparative analysis in Chapter 3 provides a more in-depth study of the legal relationship between the custodian of a biobank and the donor as well as their respective rights and obligations.

This PhD project looked at many different types of biobanks and biobank networks (as described in the introduction). It furthermore studied the legal framework applicable to various uses of HBM and data in the framework of scientific research. This allowed us to gain a broad insight into the topic of access to biobanks. It did not allow considering all details applicable to particular types of biobanks. It could be useful to focus future studies on a particular type of biobank. Separate studies could concentrate on, for instance, disease-oriented or population based biobanks. Another possibility could be to focus on the use of HBM and data for a particular type of research, such as research on cancer or particular genetic disorders. This could allow a more in-depth understanding of a particular type of biobank or use of HBM and data.

3.1 Harmonization across biobank initiatives

Chapter 1 of this PhD project lists our findings on a comparative document analysis of publicly available access arrangements. We analysed the access arrangements of 26 organizations, 36 biobank networks and 20 biobanks worldwide. The results of the comparative analysis are not generalizable, since we only compared a selection of access arrangements. A literature review allowed us to identify 21 key conditions in relation to access to HBMs and data. Our analysis focused on these 21 key conditions. We cannot exclude that other conditions might become equally relevant for access to biobanks. Information on the 21 key conditions was summarized and compared using predefined templates. Access arrangements did not always explicitly refer to one or more of the 21 access conditions under study (as explained in this study by the lack of clarity of the terminology). Whenever this was the case, we interpreted the text of the arrangement to discover implicit information on the access conditions. It was however not possible to enquire for each biobank initiative whether our interpretations fully correspond with the real (unexpressed) intentions of the concerned biobank initiative. The comparative analysis allowed us to study a considerable amount of access arrangements. It did not allow us to make an in-depth study of all policies of the concerned biobank initiatives. We are furthermore aware of the fact that access arrangements only represent the publicly available policy information of a biobank initiative. They do not present information on the actual (often not public) access practices of biobank initiatives. That is why interviews were conducted with

stakeholders and experts in the second empirical study. In the course of the study we realized that quite a lot of access arrangements do not contain any information on several key access conditions. This made it more difficult to compare the access arrangements. It also made it more difficult to come to generalizable conclusions on the extent of harmonization.

3.2 Custodianship on HBM and data stored in biobanks

Another limitation is related to the sample of interviewees included in the second chapter of the PhD, namely the empirical study of access practices. We conducted interviews with 28 stakeholders and experts in the Benelux, Denmark, Norway and Sweden. The main purpose of the sampling of interviewees was to capture perspectives of different types of stakeholders and experts. That is why we interviewed both legal and ethical experts, custodians of biobanks, representatives of biobank networks, academic, clinical and industrial (research) applicants and patient representatives. The majority of the informants were interviewed in Belgium. A more limited number of informants were interviewed in Denmark (2), Luxemburg (1), the Netherlands (2), Sweden (2) and Norway (2). We noticed that some informants fulfilled a double role, such as applicant and representative of stakeholders within an access committee. The interviewers took those double roles into account in the analysis, but focused on the main role of the informant. During the analysis of the interviews we discovered fewer variations in opinion than we would have expected. We were also not able to contribute variations of opinions to specific types of stakeholders or experts. The fact that we discovered fewer variations might be due to the fact that we were only able to interview 28 informants. It might also be due to the fact that some topics discussed during the interviews were relatively new to some of the informants.

3.3 Legal framework governing access and use of HBM and data for research purposes

Chapter 3 of the PhD aimed to compare the national legal framework applicable to access to biobanks in Belgium and normative documents at the international level and at the level of the Council of Europe. It also compared the applicable legal framework in Belgium and Denmark. Comparing those different legal documents cannot provide a complete answer to the question which rights and obligations are held by the custodian, the applicant and the donor. First, we could only study the main international normative instruments that are relevant to “access to biobanks”, due to the abundance of instruments that might be relevant to biobanks. Second, the scope and the binding force of the legal documents are different. Only the studied national legislations create legal enforceable rights and obligations. The international normative documents rather provide general principles and guidance on access to biobanks. Finally we studied two legal documents that did not enter into force yet. The legal provisions on biobanks in the Belgian Act on HBM have been modified several times and have still not entered into force. The new Minister of Health furthermore indicated in her policy note that the legal provisions on biobanks will be further modified and improved. One or more Royal Decrees executing the future provisions on biobanks are still pending. It is therefore no surprise that the literature on the future legal provisions on biobanks in Belgium is rather limited. We also studied the most important

modifications suggested to the Recommendation (2006)4[110] in the Working document on research on biological materials of human origin (hereafter the "Working Document'"). The final text of the modifications to Recommendation (2006)4 has not been published yet. We nevertheless decided to include the Working Document in the legal analysis, since a lot of the new provisions suggested in the Working Document relate specifically to access to biobanks.

3.4 IPRS in biobanking: challenges and opportunities for translational research

Chapter 4 of the PhD reports on a literature review on intellectual property rights in biobanking and to a lesser extent on the sharing of benefits and the sharing and return of research results. We concentrated on the question how to address and manage IPRs and the sharing of benefits and research results in the access arrangements of biobanks. This chapter provides input for a discussion on strategies and options for publicly funded biobanks with regard to this question. The strategies and options exposed in this chapter are, however, not supported by empirical data.

4 Future perspectives

This PhD project studied in an interdisciplinary manner whether the existing legal framework corresponds to the needs of biobanks and other stakeholders.

We quickly came to realize that the concepts of 'biobanks' and 'biobank networks' represent a heterogeneous group of infrastructures. It is therefore not so straightforward to formulate uniform rules on access to biobanks in general.

We also noticed that the discipline of biobanking is still relatively young(25). Many countries are still developing new biobank infrastructures. This might explain why several access arrangements of biobank initiatives (studied in Chapter 1) did not contain information on several key access conditions. Many biobanks initiatives will presumably develop further their access arrangements. One can refer in this respect to recent initiatives of, for instance, P^3G(77,163). Some biobank initiatives increasingly exchange experiences on practical matters related to biobanking but also on legal knowledge. We hope this PhD can contribute to these efforts.

In November 2014 BBMRI-ERIC announced the creation of a European Centre for Ethical, Legal and Social Issues (ELSI) on biobanking. Such European Centre will provide common services on Ethical, Legal and Social Issues to the members of BBMRI-ERIC. One can expect that this will generate new opportunities to develop code of conducts, guidelines or best practices on access to biobanks. Those opportunities might even lead to an increased harmonisation of the European legal framework applicable to biobanks. In addition, BBMRI-ERIC is about to start a Stakeholder forum to align interests of different stakeholders in the context of biobanking.

[110] The Recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin

The legal study (Chapter 3) showed that the legal framework on biobanks is still evolving. One can refer in this respect to the fact that the future provisions on biobanks in the Belgian Act on HBM have not entered into force yet. The Minister of Health Furthermore, furthermore, announced in her policy note that the provisions on biobanks will further be developed and improved in consultation with the stakeholders.

Recommendation (2006)4[111] of the Council of Europe is furthermore under revision. The final text of the modifications to Recommendation (2006)4 have not been published yet. We nevertheless noticed that the Working Document[112] published by the Committee of Bioethics suggests a lot of new provisions that specifically relate to access to biobanks.

Taken into account the evolving nature of biobanks, we hope that this PhD project can be inspiring to these recent legal developments and may contribute to the creation of a clear and smooth legal framework on access to biobanks.

[111] The Recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin

[112] The Working document on 'research on biological materials of human origin' was published by the Committee on Bioethics – an intergovernmental body within the Council of Europe – on 18 March 2014

Summary

The European Strategy Forum on Research Infrastructures (ESFRI) identified biobanks as one of the main priority research infrastructures for the European Research Area (ERA) for the next 10 to 20 years(8). Millions of human biological material (HBM) and associated data are collected each year for a variety of purposes. These purposes may include basic research studies, clinical trials and epidemiological studies(11,12).

The legal framework that determines access to biobanks remains unclear. The absence of a defined set of applicable rules creates legal uncertainty for biobanks and applicants. The PhD project studied the legal framework that determines the relationship between a biobank and a researcher that applies for access to HBM and data stored in a biobank. In an interdisciplinary context, the PhD project aims to contribute to the creation of a clear and smooth legal framework – i.e. legislation, non-binding normative instruments and access arrangements – applicable to biobanks.

The general introduction provides a deeper insight into the use of HBM and associated data for research purposes. First, it highlighted the importance of biobanks for biomedical research. Second, it looked at different types of HBM and data collected for research purposes. Third, it described the different research purposes to collect and use HBM and data. Finally, it dug deeper into the definition of the terms ‘biobanks’ and ‘biobank networks’.

The first chapter of the PhD reports on a comparative analysis of access arrangements of organizations, biobank networks and biobanks. The comparative analysis revealed a lack of harmonization on how access conditions are defined and implemented. A considerable number of access arrangements did not contain clear information on how the biobank initiatives (should) implement several of the studied access conditions. The lack of clear information on access conditions could hinder access to biobanks and biobank networks(14,16,63,69,77,81,82,84,91). The analysis did reveal a trend to grant custodianship to biobanks or biobank networks and no longer to individual collectors or principal investigators. This can be explained by the fact that biomedical research requires access to large amounts of HBM and data of high quality(23,65,81,91). Finally the comparative analysis confirmed that the majority of the biobank initiatives establishes an access committee to evaluate requests for access to HBM and data. The mandate of such access committees is not always clearly defined.

The second chapter of the PhD reports on an empirical study of access practices in the context of biobanking. Interviews were conducted with stakeholders and experts to gather qualitative data on the different perspectives held by stakeholders in relation to the rights and obligations of custodians and applicants with respect to access to HBM and data stored in biobanks. The first part of the semi-structured interviews focused on the evaluation of access requests by access committees. The interviews raised the importance of clarifying the interaction between research ethics committees and access committees of biobanks (105).

There was no consensus among the interviewees on whether and to which extent access committees of biobanks should evaluate the quality, the scientific and medical usefulness and the ethical value of research projects. The interviewees did agree that access committees should only evaluate access requests on the condition that they dispose of sufficient expertise, experience and independence(11,23,105,106). The interviewees felt that similar evaluation criteria should apply to academic and non-academic applicants. Following the interviews, there is no doubt that applicants need to obtain the approval from the access committee of a biobank – and a research ethics committee – to use leftover HBM in a new project.

The access fees charged by biobanks are often insufficient to compensate all costs in relation to the collection, storage and distribution of HBM and data for research purposes. Two interviewees raised the need to develop new mechanism to feed some of the benefits of biomedical research back into the biobank infrastructure and the health care system(23,111). Public biobanks could charge a higher access fee to industrial or external applicants – compared to internal applicants – for the access to a publicly funded collection of HBM and data(16,25).

There was consensus among the interviewees that an applicant could be required to share his research results with the biobank and/or other researchers. One should however protect the legitimate interests of the researcher that generated the research results.

Today, quite some collections of HBM and data are established at the initiative of the principal investigators of specific research projects. Furthermore biobanks still rely on individual clinicians or researchers for the collection of specific HBM and data. Biobank initiatives could recognize such contribution by granting a temporary priority right to conduct research with the collected HBM and data(16,106).

The third chapter of the PhD reports on a comparative study of the legal framework applicable to access to biobanks. The comparative study started with description and analysis of the legal framework applicable to access to biobanks in Belgium and Denmark, at the international level and at the level of the Council of Europe. Subsequently it compared the different legal frameworks applicable to access to biobanks. The conclusion summarized to which extent the rights and obligations of the custodian and the applicant are regulated via the existing legal framework.

The legal study in Chapter 3 shows that the Belgian legislation applicable to biobanks mainly focuses on the rights and obligations of the donor and the custodian. Fewer provisions relate to the rights and obligations of the applicants. The Belgian and Danish legislation applicable to biobanks do not contain any provisions on the mandate of an access committee. Some international normative instruments provide additional guidance on the role of an access committee and the development of access policies, procedures and mechanisms. The OECD Guidelines for Human Biobanks and Genetic Research Databases (36) formulate the general principle that biobanks should develop policies on the commercialization of HBM and data, intellectual property rights (IPRs), the sharing in scientific advancements and its benefits and the sharing of research results.

The fourth chapter of the PhD reports on a legal study on IPRs in biobanking and on the return and sharing of research results. This study discusses the risks and opportunities associated with the identified IPRs for an effective protection and use of biobanks in translational research and innovation. The study concluded that an IPR policy may be used as a tool to enhance the acknowledgement and protection of the interests of the biobank. Such policy may also be used to stimulate the development of biobanks as essential research tools or infrastructures(150). However, one should avoid that IPRs would become an obstacle to the use of HBM and data in research projects. Chapter 4 tackled the question of how to address and manage IPRs directed to HBM and data stored in the biobank and the results of research using the HBM and associated data. We looked amongst others into the question whether biobanks should be involved in upstream and downstream IPRs. Finally the chapter highlights how biobanks could be involved in the development of policies on the sharing of research results.

The fifth chapter of the PhD formulates concluding findings and recommendations on the legal framework applicable to biobanks. First, we conclude that an optimal legal framework combines legislation, soft law and access arrangements. Second, we recommend that biobanks should develop clear policies on the evaluation of access requests. Third, we suggest that biobanks clearly define the conditions under which industrial companies can access publicly funded collections of HBM and data. Fourth, we draw the attention to the importance of recognizing the contributions of individual collectors to the collections of HBM and associated data. Fifth, we recommend that biobank initiatives would develop a policy on the sharing of research results. Sixth, biobanks are invited to develop a policy on IPRs. Finally, we highlight the importance of involving donors and patients in the access policies of biobanks.

Samenvatting

Het Europees Strategisch Forum inzake de onderzoeksinfrastructuur heeft biobanken geïdentificeerd als een van de belangrijkste prioritaire onderzoeksinfrastructuren voor de Europese Onderzoeksruimte in de komende 10 tot 20 jaar (8). Elk jaar worden miljoenen stalen menselijk lichaamsmateriaal (MLM) en daarmee samenhangende gegevens verzameld voor verschillende doeleinden. Deze doeleinden hebben onder meer betrekking op fundamenteel onderzoek, klinische proeven en epidemiologische studies (11,12).

Het juridisch kader dat de regels inzake toegang tot biobanken bepaalt, blijft onduidelijk. Het ontbreken van een duidelijk gedefinieerd kader leidt tot rechtsonzekerheid. Het doctoraatsonderzoek bestudeerde het juridische kader dat van toepassing is op de relatie tussen een biobank en een onderzoeker die een aanvraag indient om toegang te krijgen tot MLM en gegevens die zijn opgeslagen in een biobank. Het doctoraatsproject heeft als doel een bijdrage te leveren aan de totstandkoming van een helder en toegankelijk juridisch kader voor biobanken. Dit juridisch kader kan bestaat uit wetgeving, juridisch niet-bindend normatieve instrumenten en toegangsregelingen.

De algemene inleiding biedt een nader inzicht in het gebruik van MLM en daarmee samenhangende gegevens voor onderzoeksdoeleinden. In de eerste plaats wordt het belang van biobanken voor biomedisch onderzoek nader toegelicht. Vervolgens worden de verschillende types van MLM en gegevens die worden verzameld voor onderzoek beschreven. Ten derde behandelt de inleiding de verschillende onderzoeksdoeleinden waarvoor MLM en data worden verzameld en gebruikt. Tot slot, gaan we dieper in op verschillende definities van de begrippen 'biobanken' en 'biobank netwerken'.

Het eerste hoofdstuk van het doctoraat brengt verslag uit van een vergelijkende analyse van toegangsregelingen van organisaties, biobank netwerken en biobanken. De vergelijkende analyse duidt op een gebrek aan harmonisatie in de wijze waarop toegangsvoorwaarden worden gedefinieerd en geïmplementeerd. Een aanzienlijk aantal van de toegangsregelingen bevatten bovendien geen duidelijke informatie over hoe biobank initiatieven een aantal van de onderzochte toegangsvoorwaarden implementeren. Het gebrek aan duidelijke informatie over de toegangsvoorwaarden kan de toegang tot biobanken en biobank netwerken belemmeren (14,16,63,69,77,81,82,84,91). De analyse bracht een trend aan het licht om het beheer van verzameling van MLM en data toe te vertrouwen aan biobanken of biobank netwerken en niet langer aan individuele verzamelaars of hoofdonderzoekers. Dit kan worden verklaard door het feit dat biomedisch onderzoek toegang vereist tot grote hoeveelheden MLM en gegevens van hoge kwaliteit (23,65,81,91). Tenslotte bevestigde de vergelijkende analyse dat de meerderheid van de biobank initiatieven een toegangscomité in het leven roepen om toegang tot MLM en gegevens te beoordelen. Het mandaat van een dergelijk toegangscomité is echter niet altijd duidelijk omschreven.

Het tweede hoofdstuk van het doctoraat bestaat uit een empirische studie inzake de toegangspraktijken toegepast door biobanken. Interviews werd uitgevoerd met belanghebbenden en deskundigen om kwalitatieve gegevens te verzamelen over de verschillende perspectieven met betrekking tot de rechten en verplichtingen van beheerders en aanvragers inzake toegang tot MLM en de gegevens die in biobanken zijn opgeslagen.

Het eerste deel van deze semigestructureerde interviews was gericht op de beoordeling van toegangsaanvragen door toegangscomités. De interviews wezen uit dat het belangrijk is om de interactie tussen ethische comités en toegangscomités (105) duidelijk te regelen. Er bestond geen consensus onder de geïnterviewden over de vraag of en in welke mate een toegangscomité de kwaliteit, het wetenschappelijk en medisch nut en de ethische waarde van onderzoeksprojecten moet evalueren. De geïnterviewden waren het er wel over eens dat de toegangscomités enkel toegangsaanvragen kunnen beoordelen, indien zij over voldoende deskundigheid, ervaring en onafhankelijkheid beschikken (11,23,105,106). De geïnterviewden waren van mening dat soortgelijke evaluatiecriteria moeten gelden voor academische en niet-academische aanvragers. De interviews bevestigden dat aanvragers in ieder geval goedkeuring dienen te verkrijgen van het toegangscomité van de biobank – en een ethisch comité – om residuair MLM te gebruiken in een nieuw project.

De toegangsvergoedingen die biobanken aanrekenen zijn vaak onvoldoende om alle kosten te compenseren met betrekking tot het verzamelen, opslaan en ter beschikking stellen van MLM en gegevens voor onderzoeksdoeleinden. Een aantal geïnterviewden identificeerden de nood om nieuwe mechanismen te ontwikkelen zodat een aantal van de voordelen van het biomedisch onderzoek terug zouden vloeien naar de biobank infrastructuur en de gezondheidszorg (23,111). Publieke biobanken zouden een hogere toegangsvergoeding kunnen aanrekenen aan externe en industriële aanvragers – in vergelijking met interne aanvragers – voor het verlenen van toegang tot publiek gefinancierde collecties van MLM en data (14,36).

Er bestond consensus onder de geïnterviewden dat een aanvrager kan worden gevraagd om zijn onderzoeksresultaten te delen met de biobank en/of andere onderzoekers. Men dient evenwel de rechtmatige belangen van de onderzoeker met betrekking tot deze onderzoeksresultaten te beschermen.

Vandaag de dag, worden heel wat collecties van MLM en data opgericht op initiatief van hoofdonderzoekers van specifieke onderzoeksprojecten. Verder rekenen biobanken nog vaak op individuele clinici en onderzoekers voor het verzamelen van specifieke MLM en data. Biobank initiatieven kunnen een dergelijke bijdrage erkennen door hen een tijdelijk prioritair recht te verlenen om het verzamelde MLM en data te gebruiken voor onderzoek (16,106).

Het derde hoofdstuk van het doctoraat gaat nader in op een vergelijkende studie van het juridisch kader dat van toepassing is op toegang tot biobanken. De vergelijkende studie begon met een algemeen overzicht van de toepasselijk nationale wetgeving in België en Denemarken, en niet-bindende normatieve normen op internationaal niveau en op het niveau van de Raad van Europa. Het hoofdstuk bestaat vervolgens uit een vergelijking tussen de verschillende juridische kaders.

De juridische studie in hoofdstuk 3 toont aan dat de Belgische wetgeving die van toepassing is op biobanken, vooral gericht is op de rechten en verplichtingen van de donor en de beheerder. De wetgeving bevat minder bepalingen met betrekking tot de rechten en verplichtingen van de aanvragers. De wetgeving in België en Denemarken bevat evenmin bepalingen over het mandaat van een toegangscomité.

Sommige internationale normatieve instrumenten bevatten wel richtlijnen inzake de rol van een toegangscomité en de ontwikkeling van een beleid, procedures en mechanismen inzake toegang tot biobanken. De OESO-richtlijnen voor 'Human Biobanks and Genetic Research Databases' (36) formuleert het algemene beginsel dat biobanken een beleid moeten ontwikkelen inzake de commercialisering van MLM en data, intellectuele eigendomsrechten (IER), het delen van wetenschappelijke vooruitgang en de vruchten daarvan, en het delen van onderzoeksresultaten.

Het vierde hoofdstuk van het doctoraat bestaat uit een juridische studie inzake het belang van IER voor biobanken en het delen van onderzoeksresultaten door onderzoekers. De studie bespreekt de risico's en opportuniteiten van de geïdentificeerde IER voor een effectieve bescherming en gebruik van biobanken in translationeel onderzoek en innovatie. Een IER beleid kan worden gebruikt als een instrument om de erkenning en bescherming van de belangen van de biobank te versterken. Ze kan ook de ontwikkeling van biobanken als essentieel onderzoeksinstrumenten of -infrastructuren (150) stimuleren. Men moet evenwel vermijden dat IER een belemmering vormen voor het gebruik van MLM en gegevens in onderzoeksprojecten. Hoofdstuk 4 gaat dieper in op de vraag hoe IER te beheren, wanneer deze betrekking hebben op MLM en gegevens die zijn opgeslagen in de biobank of met de resultaten van onderzoek met behulp van de MLM en bijbehorende gegevens. We bestudeerden onder meer de vraag of biobanken moeten worden betrokken bij 'upstream' en 'downstream' IER. Tenslotte belicht het hoofdstuk hoe biobanken betrokken kunnen worden bij de ontwikkeling van een beleid inzake het delen van onderzoeksresultaten.

Het vijfde hoofdstuk van het doctoraat formuleert een aantal conclusies en bevat een aantal aanbevelingen inzake het juridisch kader van toepassing op biobanken. Vooreerst, kunnen we concluderen dat een optimaal juridisch kader bestaat uit een combinatie van wetgeving, niet-bindende normatieve normen en toegangsregelingen. Ten tweede, raden wij biobanken aan een duidelijk beleid te ontwikkelen inzake de evaluatie van toegangsaanvragen. Ten derde, raden we biobanken aan de voorwaarden duidelijk te definiëren waaronder industriële bedrijven toegang kunnen hebben tot publiek gefinancierde collecties van MLM en data. Ten vierde, vestigen wij de aandacht op het belang om de bijdragen van de individuele verzamelaars tot de collecties van MLM en bijbehorende gegevens te erkennen. Ten vijfde, raden wij aan dat biobank initiatieven een beleid zouden ontwikkelen inzake het delen van onderzoeksresultaten. Ten zesde, moedigen we biobanken aan om een beleid inzake IER te ontwikkelen. Tenslotte benadrukken we het belang om donoren en patiënten te betrekken in het toegangsbeleid van biobanken.

References

1. Morente MM, Cereceda L, Luna-Crespo F, et al. Managing a Biobank Network. Biopreserv Biobank. 2011 Jun;9(2):187–90.

2. Yassin R, Lockhart N, González del Riego M, et al. Custodianship as an ethical framework for biospecimen-based research. Cancer Epidemiol Biomarkers Prev. 2010 Apr [cited 2014 Mar 4];19(4):1012–5.

3. NCI Best Practices for Biospecimen Resources [Internet]. 2011 p. 85. Available from: http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf

4. P3G Sample and data Access Policy: Core Elements [Internet]. P3G; 2008. Available from: http://www.p3gobservatory.org/download/P3G Sample and Data Access_SEW.doc

5. Parks A. 10 Ideas Changing the World Right Now- Biobanks. Time Magazine. 2009;

6. Biobanks for Europe: A challenge for governance. Luxembourg; 2012 p. 62. Available from

7. Biological and Medical Sciences: Roadmap Working Group: Report 2008. Brussels; 2008 p. 1–139. Available from

8. Report of the Expert Group on Research Infrastructures: A vision for strengthening world class research infrastructures on the ERA. 2010. Available from

9. Asslaber M, Zatloukal K. Biobanks: transnational, European and global networks. Brief Funct Genomic Proteomic. Zatloukal, K., Institute of Pathology, Medical University of Graz, A-8036 Graz, Austria; 2007 Sep [cited 2014 Mar 4];6(3):193–201.

10. Yuille M, van Ommen G-J, Brechot C, et al. Biobanking for Europe. Brief Bioinform. Yuille, M., The University of Manchester, School of Translational Medicine, CIGMR, Manchester M13 9PT, United Kingdom; 2008;9(1):14–24.

11. Vaught J, Lockhart NC. The evolution of biobanking best practices. Clin Chim Acta. Elsevier B.V.; 2012 Oct 9 [cited 2014 Mar 4];413(19-20):1569–75.

12. Czerepak E a., Ryser S. Drug approvals and failures: implications for alliances. Nat Rev Drug Discov. 2008 Mar [cited 2013 Feb 1];7(3):197–8.

13. Vaught JB, Henderson MK, Compton CC. Biospecimens and biorepositories: from afterthought to science. Cancer Epidemiol Biomarkers Prev. 2012 Feb [cited 2014 Dec 2];21(2):253–5.

14. Cadigan RJ, Easter MM, Dobson AW, et al. “That’s a good question”: university researchers’ views on ownership and retention of human genetic specimens. Genet Med. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA: LIPPINCOTT WILLIAMS & WILKINS; 2011 Jun;13(6):569–75.

15. Meir K, Gaffney EF, Simeon-Dubach D, et al. . Biopreserv Biobank. 2011;9(3):279.

16. Fortin S, Pathmasiri S, Grintuch R, et al. “Access arrangements” for biobanks: a fine line between facilitating and hindering collaboration. Public Health Genomics. Deschenes, M., P3G Consortium, Montreal, QC H3V 1A2, Canada; 2011 Jan [cited 2014 Mar 4];14(2):104–14.

17. Edwards T, Cadigan RJ, Evans JP, et al. Biobanks containing clinical specimens: defining characteristics, policies, and practices. Clin Biochem. Elsevier B.V.; 2014 Mar 15 [cited 2014 Jun 15];47(4-5):245–51.

18. Gottweis H, Zatloukal K. Biobank governance: trends and perspectives. Pathobiology. 2007 Jan [cited 2011 May 31];74(4):206–11.

19. Advice no. 45 of 19 January 2009 concerning banks of human bodily material for research purposes. 2009 p. 1–33. Available from

20. Bell WC, Sexton KC, Grizzle WE. Organizational issues in providing high-quality human tissues and clinical information for the support of biomedical research. Methods Mol Biol. 2010 Jan [cited 2011 May 31];576:1–30.

21. Hasan S. The Increasing Role of Biobanks in Personalized Medicine [Internet].

22. Donato J. Biobanking for Rare Diseases - Impact on Personalised Medicine. In: Özgüç M, editor. Rare Diseases: Integrative PPPM Approach as the Medicine of the Future. Dordrecht: Springer Netherlands; 2015 [cited 2014 Dec 20]. p. 23–31.

23. Cambon-Thomsen A, Rial-Sebbag E, Knoppers BM. Trends in ethical and legal frameworks for the use of human biobanks. Eur Respir J. 2007 Aug [cited 2014 Mar 4];30(2):373–82.

24. Godard B, Schmidtke J, Cassiman J, et al. Data Storage and DNA Banking for Biomedical Research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective". Eur J Hum Genet. 2003;11(Suppl 2):S88–122.

25. Riegman PHJ, Morente MM, Betsou F, et al. Biobanking for better healthcare. Mol Oncol. Riegman, P.H.J., Department of Pathology, Josephine Nefkens Institute, Erasmus Medical Center, 3015 GE Rotterdam, Netherlands; 2008 Oct [cited 2014 Mar 4];2(3):213–22.

26. Hewitt RE. Biobanking: The foundation of personalized medicine. Curr Opin Oncol. Hewitt, R. E., 13100 Aix-en-Provence, France; 2011;23(1):112–9.

27. Riegman PHJ, van Veen E-B. Biobanking residual tissues. Hum Genet. 2011 Sep [cited 2013 Nov 29];130(3):357–68.

28. Linsen L, Hensen K, Rummens J-L (Virga J. Biobanken: Bouwstenen voor translationeel onderzoek. Virghaal Wet. 2009;2.

29. Brisson AR, Matsui D, Rieder MJ, et al. Translational research in pediatrics: tissue sampling and biobanking. Pediatrics. 2012 Jan [cited 2014 Dec 2];129(1):153–62.

30. Andersson K, Bray F, Arbyn M, et al. The interface of population-based cancer registries and biobanks in etiological and clinical research - current and future perspectives. Acta Oncol. 2010 Nov [cited 2010 Oct 27];49(8):1227–34.

31. Zielhuis G a. Biobanking for epidemiology. Public Health. Elsevier Ltd; 2012 Mar 9 [cited 2014 Dec 20];126(3):214–6.

32. Almqvist C, Adami H-O, Franks PW, et al. LifeGene - A large prospective population-based study of global relevance. Eur J Epidemiol. Almqvist, C., Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, Stockholm SE-171 77, Sweden; 2011;26(1):67–77.

33. Elger BS, Caplan AL. Consent and anonymization in research involving biobanks: differing terms and norms present serious barriers to an international framework. EMBO Rep. 2006 Jul [cited 2011 May 31];7(7):661–6.

34. Hewitt R, Watson P. Defining Biobank. Biopreserv Biobank. 2013 Oct;11(5):309–15.

35. Nys H. Bloed, zweet en tranen. Kritische ontleding van de wet van 19 december 2008 inzake het verkrijgen en het gebruik van menselijk lichaamsmateriaal. Rechtskundig Weekbl. 2009;(5):178–89.

36. OECD Guidelines on Human Biobanks and Genetic Research Databases. 2009.

37. Commission Implementing Decision of 22 November 2013 on setting up the Biobanks and Biomolecular Resources Research Infrastructure Consortium (BBMRI-ERIC) as a European Research Infrastructure Consortium. 2013 p. 63–80.

38. Legislation on biotechnology in the Nordic countries. 2014 p. 51. Available from

39. Petersen J. Biobanks and the Law in Denmark. Eur Intellect Prop Rev. 2004;383–9.

40. Recommendation 2006(4) of the Committee of Ministers to member states on research on biological materials of human origin. Council of Europe; 2006. p. 6.

41. Tutton R. Banking expectations: the promises and problems of biobanks. Per Med. Tutton, R., Lancaster University, Centre for the Economic and Social Aspects of Genomics (CESAGen), Institute for Advanced Studies, Lancaster LA1 4YD, United Kingdom; 2007 Nov [cited 2014 Apr 16];4(4):463–9.

42. Sak J, Pawlikowski J, Goniewicz M, et al. Population biobanking in selected European countries and proposed model for a Polish national DNA bank. J Appl Genet. 2012 Jan 27 [cited 2012 Mar 11];

43. Ollier W, Sprosen T, Peakman T. UK Biobank: from concept to reality. Pharmacogenomics. 2005 Sep [cited 2014 Dec 3];6(6):639–46.

44. Barbareschi M, Fasanella S, Cantaloni C, et al. Scientific and Managerial Premises and Unresolved Issues in Tumour Biobanking Activities. In: Pascuzzi G, Izzo U, Macilotti M, editors. Comparative Issues in the Governance of Research Biobanks: Property, Privacy and Intellectual Property, and the Role of Technology. Trento: Springer; 2013. p. 301–10.

45. Shickle D, Griffin M, El-Arifi K. Inter- and intra-biobank networks: classification of biobanks. Pathobiology. Shickle, D., Academic Unit of Public Health, Institute of Health Sciences, University of Leeds, Leeds LS2 9LJ, United Kingdom; 2010 Jan;77(4):181–90.

46. Bergmann MM. The EPIC study – data, samples and ethical challenges. Leuven; 2012.

47. Tybring G. Managing and Using a Biobank in Sweden [Internet]. 2013. p. 24.

48. Van den Eynden J, Degaillier C, Van Eycken L, et al. the Belgian Virtual Tumourbank a tool for translational cancer research. Biopreserv Biobank. 2011;9(3):292.

49. Bekaert S, Ectors N, in't Veld P, et al. Multidisciplinary working groups around the Flemish Biobank stimulates the Translational Biomedical Research, Poster at ESBB Conference 2014. Leipzig; 2014. p. 1.

50. Welcome to the European Cancer Sample Exchange Platform [Internet].

51. Riegman PHJ, de Jong BWD, Llombart-Bosch A. The Organization of European Cancer Institute Pathobiology Working Group and its support of European biobanking infrastructures for translational cancer research. Cancer Epidemiol Biomarkers Prev. 2010 May [cited 2011 May 31];19(4):923–6.

52. Groen licht vier nieuwe parels [Internet].

53. Talmon JL, Ros MG, Legemate DA. PSI: The Dutch Academic Infrastructure for shared biobanks for translational research. Transl Bionforma. 2008 Jun;110–4.

54. Ectors N. International and national initiatives in biobanking. Verh K Acad Geneeskd Belg. 2011 Jan [cited 2012 Feb 8];73(1-2):5–40.

55. Thirlway H. The Sources of International Law. Oxford: Oxford University Press; 2014.

56. Platt J, Bollinger J, Dvoskin R, et al. Public preferences regarding informed consent models for participation in population-based genomic research. Genet Med. 2014 Jan [cited 2014 Mar 4];16(1):11–8.

57. Kerath SM, Klein G, Kern M, et al. Beliefs and attitudes towards participating in genetic research - a population based cross-sectional study. BMC Public Health. 2013;13:114.

58. Cervo S, Rovina J, Talamini R, et al. An effective multisource informed consent procedure for research and clinical practice: an observational study of patient understanding and awareness of their roles as research stakeholders in a cancer biobank. BMC Med Ethics. BMC Medical Ethics; 2013 Jan [cited 2014 Jan 10];14(1):30.

59. Chen H, Gottweis H, Starkbaum J. Public Perceptions of Biobanks in China: A Focus Group Study. Biopreserv Biobank. 2013 Oct [cited 2013 Nov 29];11(5):267–71.

60. Gottweis H, Gaskell G, Starkbaum J. Connecting the public with biobank research: reciprocity matters. Nat Rev Genet. Nature Publishing Group; 2011 Jan [cited 2011 Oct 21];12(11):738–9.

61. Gaskell G, Gottweis H, Starkbaum J, et al. Publics and biobanks: Pan-European diversity and the challenge of responsible innovation. Eur J Hum Genet. 2013 Jan [cited 2013 May 22];21(1):14–20.

62. Schildmann J, D'Abramo F, Vollmann J. Information and consent in biobanking research. A review of socio-empirical research on the views and preferences of research participants and the public. Onkologie. 2013;36(Supplement 7):200–1.

63. Vaught J, Kelly A, Hewitt R. A review of international biobanks and networks: Success factors and key benchmarks. Biopreserv Biobank. Vaught, J., Office of Biorepositories and Biospecimen Research (OBBR), National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, United States; 2009;7(3):143–50.

64. Hens K, Nys H, Cassiman J-J, et al. Biological sample collections from minors for genetic research: a systematic review of guidelines and position papers. Eur J Hum Genet. 2009 Aug [cited 2014 Mar 4];17(8):979–90.

65. Bauer K, Taub S, Parsi K. Ethical issues in tissue banking for research: a brief review of existing organizational policies. Theor Med Bioeth. 2004 Jan [cited 2014 Mar 4];25(2):113–42.

66. Master Z, Nelson E, Murdoch B, et al. Biobanks, consent and claims of consensus. Nat Methods. Nature Publishing Group; 2012 Sep 30 [cited 2014 Mar 4];9(9):885–8.

67. Henderson GE, Edwards TP, Cadigan RJ, et al. Stewardship Practice of U.S. Biobanks. Sci Transl Med. 2013;5(215):1–6.

68. Crawford G, Foulds N, Fenwick A, et al. Genetic medicine and incidental findings: it is more complicated than deciding whether to disclose or not. Genet Med. 2013 Nov [cited 2014 Mar 4];15(11):896–9.

69. Access to collections of data and materials for health research: A report to the Medical Research Council and the Wellcome Trust [Internet]. Medical Research Council and the Wellcome Trust; 2006. Available from: http://www.wellcome.ac.uk/About-us/Publications/Reports/Biomedical-ethics/WTX030843.htm

70. Scott CT, Caulfield T, Borgelt E, et al. Personal medicine--the new banking crisis. Nat Biotechnol. Nature Publishing Group; 2012 Feb 8 [cited 2014 Mar 4];30(2):141–7.

71. Fleiner T. Common Law and Continental Law : Two Legal Systems. 2005. p. 1–35.

72. Dyèvre A. Realism About Legal Integration : Outline of a Nuanced Legal Realist Approach. 2013 p. 1–25. Available from

73. Pukkala E, Andersen A, Berglund G, et al. Nordic biological specimen banks as basis for studies of cancer causes and control - More than 2 million sample donors, 25 million person years and 100 000 prospective cancers. Acta Oncol (Madr). Pukkala, E., Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, FI-00170 Helsinki, Finland; 2007;46(3):286–307.

74. Frank L. The Epidemiologist ’s Dream : Denmark. Science (80-). 2003;301:70.

75. Kaye J. Do we need a uniform regulatory system for biobanks across Europe? Eur J Hum Genet. 2006 Mar [cited 2011 May 31];14(2):245–8.

76. Material and Data Access Agreement- Core Elements and Generic Clauses [Internet]. P3G; 2008 p. 6. Available from: http://www.p3gobservatory.org/repository/ethics.htm

77. Knoppers BM, Chisholm RL, Kaye J, et al. A P3G generic access agreement for population genomic studies. Nat Biotechnol. Nature Publishing Group; 2013 May [cited 2014 Mar 4];31(5):384–5.

78. Zatloukal K, Vaught J. What Are the Next Steps to Overcoming Roadblocks to Transnational Biobank Collaboration? Biopreserv Biobank. 2012 Feb [cited 2012 Feb 27];10(1):2–3.

79. Watson PH, Ravid R, Eng CB, et al. What Are the Main Roadblocks to Transnational Biobank Collaboration, and How Can We Overcome Them? Biopreserv Biobank. 2011 Sep [cited 2011 Dec 2];9(3):213–6.

80. Lopez-Guerrero JA, Riegman PHJ, Oosterhuis JW, et al. TuBaFrost 4: access rules and incentives for a European tumour bank. Eur J Cancer. 2006 Nov [cited 2014 Mar 4];42(17):2924–9.

81. Lemrow SM, Colditz GA, Vaught JB, et al. Key elements of access policies for biorepositories associated with population science research. Cancer Epidemiol Biomarkers Prev. 2007 Aug [cited 2014 Mar 4];16(8):1533–5.

82. Joly Y, Zeps N, Knoppers BM. Genomic databases access agreements: legal validity and possible sanctions. Hum Genet. 2011 Jun 25;130(3):441–9.

83. Creation and Governance of Human Genetic Research Databases [Internet]. OECD; 2006. Available from: http://www.oecd.org/science/biotech/creationandgovernanceofhumangeneticresearchdatabases.htm

84. Colledge F, Elger B, Howard HC. A Review of the Barriers to Sharing in Biobanking. Biopreserv Biobank. 2013 Dec [cited 2014 Jan 17];11(6):339–46.

85. Campbell LD, Betsou F, Garcia DL, et al. Development of the ISBER Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research. Biopreserv Biobank. 2012 Apr [cited 2012 May 7];10(2):232–3.

86. Principles and Guidelines for Access to Research Data from Public Funding [Internet]. OECD; 2007. Available from: http://www.oecd.org/science/sci-tech/38500813.pdf

87. Wichmann H-E, Kuhn K a, Waldenberger M, et al. Comprehensive catalog of European biobanks. Nat Biotechnol. 2011 Sep [cited 2014 Jan 22];29(9):795–7.

88. Human biobanks for research: Opinion [Internet]. Berlin: Deutscher Ethikrat; 2010. Available from: http://www.ethikrat.org/dateien/pdf/stellungnahme-humanbiobanken-fuer-die-forschung.pdf

89. Zika E, Paci D, Schulte in den Bäumen T, et al. Biobanks in Europe: Prospects for Harmonisation and Networking. 2010 p. 170. Available from

90. Watson RWG, Kay EW, Smith D. Integrating biobanks: addressing the practical and ethical issues to deliver a valuable tool for cancer research. Nat Rev Cancer. 2010 Sep 12 [cited 2014 Mar 4];10(9):646–51.

91. O'Brien SJ. Stewardship of human biospecimens, DNA, genotype, and clinical data in the GWAS era. Annu Rev Genomics Hum Genet. 2009 Jan [cited 2014 Mar 4];10(May):193–209.

92. Hakimian R, Korn D. Ownership and use of tissue specimens for research. JAMA. 2004 Nov 24 [cited 2014 Mar 4];292(20):2500–5.

93. All for one and one for all. Nat Methods. 2009 Feb [cited 2014 Dec 2];6(2):111–111.

94. Quigley M. Property and the body: applying Honore. J Med Ethics. 2007 Nov [cited 2014 Mar 4];33(11):631–4.

95. Björkman B. Different types--different rights. Distinguishing between different perspectives on ownership of biological material. Sci Eng Ethics. 2007 Jun [cited 2014 Mar 4];13(2):221–33.

96. Samples and data for research: Template for access policy development [Internet]. National Cancer Research Institute, the National Cancer Intelligence Network and onCorde UK; 2009 p. 45. Available from: http://www.oncoreuk.org/pages/researchers_data.html

97. Milanovic F, Pontille D, Cambon-Thomsen A. Biobanking and Data Sharing: A Plurality of Exchange Regimes. Genomics, Soc Policy. 2007;3:17–30.

98. Fullerton SM, Anderson NR, Guzauskas G, et al. Meeting the governance challenges of next-generation biorepository research. Sci Transl Med. 2010 Jan 20;2(15):1–8.

99. Winickoff DE, Winickoff RN. The charitable trust as a model for genomic biobanks. N Engl J Med. 2003 Oct 18 [cited 2011 May 31];349(12):1180–4.

100. Conley JM, Mitchell R, Cadigan RJ, et al. A Trade Secret Model for Genomic Biobanking. J Law Med Ethics. 2012 Sep [cited 2012 Dec 6];40(3):612–29.

101. Haddow G, Laurie G, Cunningham-Burley S, et al. Tackling community concerns about commercialisation and genetic research: A modest interdisciplinary proposal. Soc Sci Med. 2007 Jan [cited 2013 May 16];64(2):272–82.

102. Lincoln YS, Guba EG. Naturalistic Inquiry. Beverly Hills: Sage; 1985.

103. Patton MQ. Qualitative evaluation and research methods. 2nd ed. Newbury Park: SAGE Publications, Inc; 1990.

104. Dierckx de Casterlé B, Gastmans C, Bryon E, et al. QUAGOL: a guide for qualitative data analysis. Int J Nurs Stud. 2012 Mar [cited 2014 Mar 24];49(3):360–71.

105. Shabani M, Borry P. From the Principles of Genomic Data Sharing to the Practices of Data Access Committees. 2014. Available from

106. Mascalzoni D, Dove ES, Rubinstein Y, et al. International Charter of principles for sharing bio-specimens and data. Eur J Hum Genet. 1] Center for Research Ethics and Bioethics Uppsala University, Uppsala, Sweden [2] Center for Biomedicine, EURAC Research, Bolzano, Italy Centre of Genomics and Policy, Mc Gill University, Montreal, Quebec, Canada Office for Rare Diseases Research, Natio; 2014 Sep 24 [cited 2014 Dec 11];(1476-5438 (Electronic)).

107. Cook. Pharmaceuticals, biotechnology and the law. Second. London: LexisNexis; 2009.

108. Boggio A. Transfer of samples and sharing of results: requirements imposed on researchers. In: Elger BS, Biller-Andorno N, Mauron A, et al., editors. Ethical and regulatory aspects of human genetic databases. Ashgate; 2008. p. 1–11.

109. Peeters M. De rol van het EU-recht op vermarkting in de (gezondheids)zorg. Vermarkting van de zorg: meer dan commercialisering alleen? Die Keure / La Charte; 2011. p. 111–62.

110. Panis S. Stamcellen en recht: een juridische analyse van wegneming tot gebruik. 2014. p. 1050.

111. Bovenberg JA. Whose tissue is it anyway? Nat Biotechnol. 2005 Aug;23(8):929–33.

112. Smith E. The Limits of Sharing: An Ethical Analysis of the Arguments For and Against the Sharing of Databases and Material Banks. Account Res. Taylor & Francis Group; 2011;18(6):357–81.

113. Ness RB. Biospecimen “ownership”: point. Cancer Epidemiol Biomarkers Prev. 2007 Feb [cited 2013 Mar 15];16(2):188–9.

114. Cambon-Thomsen A, Thorisson G a, Andrieu S, et al. The role of a bioresource research impact factor as an incentive to share human bioresources. Nat Genet. Nature Publishing Group; 2011 Jun [cited 2011 Jun 14];43(6):503–4.

115. Kosseim P, Dove ES, Baggaley C, et al. Building a data sharing model for global genomic research. Genome Biol. 2014 Aug 11 [cited 2014 Oct 16];15(8):430.

116. Knoppers BM, Harris JR, Tassé AM, et al. Towards a data sharing Code of Conduct for international genomic research. Genome Med. 2011;3(7):46.

117. Sharing Data from Large-scale Biological Research Projects: A System of Tripartite Responsibility. 2003 p. 6. Available from

118. Creating a Global Alliance to Enable Responsible Sharing of Genomic and Clinical Data. 2013 p. 34. Available from

119. Framework for Responsible Sharing of Genomic and Health-Related Data [Internet]. Global Alliance for Genomics and Health; 2013. Available from: http://genomicsandhealth.org/framework

120. Panis S, Van Gelder N. De Wet Menselijk Lichaamsmateriaal van 19 december 2008 : een grondige analyse. Tijdschr voor Gezondheidsr. 2008;(4):217–53.

121. Coëffé M, Callens S. Le matériel corporel humain. Waterloo: Wolters Kluwer Belgium SA; 2012.

122. De Bot D. Art. 21 Wet Persoonsgegevens. Personen- en familierecht Artikelsgewijze commentaar met overzicht van rechtspraak en rechtsleer. 2001. p. 5.

123. DE BOT D. Art. 22 Wet Persoonsgegevens. Personen- en familierecht Artikelsgewijze commentaar met overzicht van rechtspraak en rechtsleer. 2001. p. 5.

124. Biobanks and the public: Governing biomedical research resources in Europe. 2013 p. 77. Available from

125. Hoeyer KL. Person, patent and property: a critique of the commodification hypothesis. Biosocieties. 2007;2(3):327–48.

126. Ravid R. Standard Operating Procedures, ethical and legal regulations in BTB (Brain/Tissue/Bio) banking: what is still missing? Cell Tissue Bank. 2008 Jun [cited 2010 Oct 21];9(2):121–37.

127. Kyvik KO. Danish biobank legislation, a simple approach ? Nor Epidemiol. 2012;21(2):161–2.

128. Hartlev M. Collecting samples for future uses Case : Opt-out in Danish Biobanking Samples for future use Stakeholders and interests. Society. Uppsala; 2011. p. 19.

129. Minssen T, Schovsbo J. Legal aspects of biobanking as key issues for personalized medicine and translational exploitation. Per Med. 2014 Jul [cited 2014 Oct 9];11(5):497–508.

130. Nicol D, Gold ER. Standards for Biobank Access and Intellectual Property. In: Rimmer M, McLennan A, editors. Intellectual Property and Emerging Technologies: The New Biology. Queen Mary. Cheltenham UK: Edward Elgar; 2012. p. 133–16.

131. Dove ES, Joly Y. The contested futures of biobanks and intellectual property. Teoría y derecho. 2012;11:132–47.

132. Caulfield T, Cook-Deegan RM, Kieff FS, et al. Evidence and anecdotes: an analysis of human gene patenting controversies. Nat Biotechnol. 2006 Sep [cited 2014 May 26];24(9):1091–4.

133. Roy AG. Protection of Intellectual Property in the Form of Trade Secrets. J Intellect Prop Rights. 2006;11(May):192–200.

134. Pathmasiri S, Deschênes M, Joly Y, et al. Intellectual property rights in publicly funded biobanks: much ado about nothing? Nat Biotechnol. Nature Publishing Group; 2011 Apr [cited 2011 Apr 14];29(4):319–23.

135. De Visscher F, Michaux B. Précis du droit d'auteur et des droits voisins. Brussels: Bruylant; 2000.

136. Vandewynckel S, Verlinden M, Meyer G. Overzicht van procesregels inzake intellectuele eigendomsrechten. Kortrijk: UGA; 2014.

137. Hellstadius A, Wolk S, Wessman R. Intellectual property and biobanks. In: Hansson MG, Levin M, editors. Biobanks as resources for health. Uppsala: Universitetstryckeriet; 2003. p. 207–25.

138. Evrard J-J, Péters P. La défense de la marque dans le Benelux - marque Benelux et marque communautaire. 2000.

139. Proposal for a Directive of the European Parliament and of the Council on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure [Internet]. Brussels; 2013 p. 26.

140. Proposal for a Directive of the European Parliament and of the Council on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure [Internet]. Brussels: Council of the European Union; 2014 p. 1–50.

141. Keshri H, Keshri S. Trade Secrets: A Secret Still to Unveil. J Intellect Prop Rights. 2008;13:208–17.

142. Minssen T, Schwartz H. Standing on shaky ground - US patent-eligibility of isolated DNA and genetic diagnostics after AMP v. USPTO - Part IV. Queen Mary J Intellect Prop. 2013;3(2):118–44.

143. Minssen T, Nilsson D. The US Supreme Court in *Mayo v Prometheus* – taking the fire *from* or *to* biotechnology and personalized medicine? Queen Mary J Intellect Prop. 2012 Dec 1;2(4):376–88.

144. Sterckx S, Cockbain J, Howard H, et al. “Trust is not something you can reclaim easily”: patenting in the field of direct-to-consumer genetic testing. Genet Med. 2013 May [cited 2014 Sep 16];15(5):382–7.

145. Simon BM, Law S, Barton J, et al. How to get a fair share: IP policies for publicly supported biobanks. Stanf J Law Sci Policy. 2008 Sep [cited 2011 Oct 17];452(2003):65–79.

146. Gitter DM. The Challenges of Achieving Open-Source Sharing of Biobank Data. Biotechnol Law Rep. 2010 Dec [cited 2014 Apr 16];29(6):623–35.

147. Henderson GE, Edwards TP, Cadigan RJ, et al. Stewardship practices of U.S. biobanks. Sci Transl Med. 2013 Dec 11 [cited 2014 Aug 25];5(215):215cm7.

148. Ducato R. “Adiós Sui Géneris”: a study of the legal feasibility of the sui generis right in the context of research biobanks [Internet]. Revista de derecho y genoma humano = Law and the human genome review / Cátedra de Derecho y Genoma Humano/Fundación BBV-Diputación Foral de Bizkaia. 2013 p. 125–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24340829

149. Verlinden M, Nys H, Ectors N, et al. Access to biobanks: harmonization across biobank initiatives. Biopreserv Biobank. 2014 Dec [cited 2014 Dec 17];12(6):415–22.

150. Pénin J, Wack J-P. Research tool patents and free-libre biotechnology: A suggested unified framework. Res Policy. 2008 Dec [cited 2014 May 26];37(10):1909–21.

151. Huys I, Matthijs G, Van Overwalle G Van. The fate and future of patents on human genes and genetic diagnostic methods. Nat Rev. Nature Publishing Group; 2012;

152. Caulfield T. Reflections on the Gene Patent War: The Myriad Battle, Sputnik and Beyond. Clin Chem. 2011;57(7):977–9.

153. Holman CM. Preliminary Thoughts on Mayo v. Prometheus: The implications for Biotechnology”. Biotechnol Law Rep. 2012;111–3.

154. Reiter TA, R. S. McQuade. Commentary: The Federal Circuit Court of Appeals decided that isolated DNA claims are patentable. Ind Biotechnol. 2011;272–5.

155. Heaney C, Carbone J, Gold R, et al. The Perils of Taking Property Too Far. Stanf J Law Sci Policy. 2009 May [cited 2014 Apr 15];1:46–64.

156. Conley JM, Vorhaus D, Cook-Deegan R. How Will Myriad Respond to the Next Generation of BRCA Testing? Genomics Law Report. 2011;4.

157. Huys I, Matthijs G, Van Overwalle G, et al. Gene and genetic diagnostic method patent claims: a comparison under current European and US patent law. EJHG. Nature Publishing Group; 2011 Jun 8 [cited 2011 Jun 28];(September 2010):1–4.

158. Holman BCM. Editorial: In Myriad the Supreme Court Has, Once Again, Increased the Uncertainty of U.S. Patent Law. Biotechnol Law Rep. 2013;32(5):289–93.

159. Andrews LB. Harnessing the Benefits of Biobanks. J Law, Med Ethics. 2005;33(1):22–30.

160. Winickoff DE. Partnership in U.K. Biobank: a third way for genomic property? J Law Med Ethics. 2007 Jan [cited 2011 May 31];35(3):440–56.

161. Feldman MP, Colaianni A, Liu CK. Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program. In: Krattiger A, Mahoney RT, editors. Intellectual property management in health and agricultural innovation: A handbook of Best Practices. 2007. p. 1797 – .

162. In the Public Interest: Nine Points to Consider in Licensing University Technology [Internet]. 2007 p. 17. Report No.: 1. Available from: http://news-service.stanford.edu/news/2007/march7/gifs/whitepaper.pdf

163. Mallete A, Tassé AM, Knoppers BM. P3G Model Framework for Biobank Governance [Internet]. Montreal; 2013 p. 1–21. Available from: http://www.p3g.org/biobank-toolkit/p3g-model-framework-biobank-governance

164. Data Access Policy for the International HapMap Project [Internet].

165. A global network for investigating the genomic epidemiology of malaria. Nature. 2008 Dec 11 [cited 2015 Jan 7];456(7223):732–7.

166. ACCESS PROCEDURES: Application and review procedures for access to the UK Biobank Resource [Internet]. 2011. p. 35.

167. O'Rourke PP, Abelman M, Heffernan KG. Centralized banks for human embryonic stem cells: a worthwhile challenge. Cell Stem Cell. 2008 Apr 10 [cited 2011 May 31];2(4):307–12.

168. Colledge FM a, Elger BS, Shaw DM. "Conferring authorship": biobank stakeholders' experiences with publication credit in collaborative research. PLoS One. 2013 Jan [cited 2015 Jan 7];8(9):e76686.

169. International Code of Conduct for Genomic and Health-Related Data Sharing. 2014 p. 8. Available from

170. OECD Best Practices Guidelines for Biological Resource Centres. 2007 p. 1–115. Available from

171. Human Tissue and Medical Research: Code of conduct for responsible use. 2011. Available from

172. Working document on research on biological materials of human origin. Strasbourg: Committee on Bioethics; 2014 p. 10.

Annexes

Annex 1: Supplementary Table to Chapter 1: Access arrangements of selected organizations, biobank networks and biobanks

Table 8: Overview of access arrangements of organizations, biobank networks and biobanks

	International organizations	Document title	Date of publication	Country
1	OECD	Principles and Guidelines for Access to Research Data from Public Funding	2007	International
bis	OECD	Guidelines on Human Biobanks and Genetic Research Databases	2009	International
2	ISBER	Best Practices for Repositories	2012	International
3	ESBB	*No access arrangement so far*	N.A.	International
4	P3G consortium	P3G Sample and Data Access (Policy): Core Elements	2009	International
bis	P3G consortium	P3G Material and Data Access Agreements: Core Elements	2009	International
5	AUTM	Uniform Biological Material Transfer Agreement	2005	International
bis	AUTM	Industry to Non-Profit Uniform Biological Material Transfer Agreement	1995	International
6	HUGO (ethics committee)	Statement on human genomic databases	2002	International
	European organizations	**Document title**	**Date of publication**	**Country**
7	Council of Europe	Recommendation (2006)4 of the Committee of Ministers to member states on research on biological materials of human origin	2006	EU
bis	Council of Europe	Convention on Human Rights and Biomedicine + additional Protocol concerning Biomedical Research	1997 & 2005	EU
8	European Society of Human Genetics	Recommendation: Data Storage and DNA Banking for biomedical research: technical, social and ethical issue	2003	EU
bis	European Society of Human Genetics	Data Storage and DNA Banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective	2003	EU
	National organizations	**Document title**	**Date of publication**	**Country**
9	Human Genetics Commission	Inside Information: Balancing Interests in the Use of Personal Genetic Information	2002	UK
10	Office of Biorepositories and Biospecimen Research, National Cancer Institute, National Institute of Health, Department of Health and Human Services	Best Practices for Biospecimen Resources	2011	US
11	Rand	Case Studies of Existing Human Tissue Repositories: Best practices for a Biospecimen Resource for the Genomic and Proteomic Era	2003	US
12	Australasian Biospecimen Network	Biorepository Protocols + section 15 'Conditions of Use' and 'Access to Biospecimens' Forms + appendix 3: National Health and Medical Research Council: Enabling grants access to facilities policy protocols	2007	Australia
13	Federa	Code of Conduct for Health Research ('Verantwoord omgaan met lichaamsmateriaal ten behoeve van wetenschappelijk onderzoek')	2011	the Netherlands
14	National Consultative Ethics Committee for Health and Life Sciences	Ethical problems raised by the collected biological material and associated information data : "biobanks"	2003	France
15	National Consultative Ethics Committee for Health and Life Sciences and Deutscher Ethikrat	Joint document of National Consultative Ethics Committee for Health and Life Sciences and Deutscher Ethikrat	2003	France and Germany

	National organizations (continued)	Document title	Date of publication	Country
16	Deutscher Ethikrat	Human biobanks for research	2010	Germany
bis	Deutscher Ethikrat	Biobanks for research	2004	Germany
17	Medical Research Council and The Wellcome Trust	Access to Collections of Data and Materials for Health Research	2006	UK
18	Medical Research Council	Human tissue and biological samples for use in research	2001	UK
19	Institut National du Cancer	Recommendations à l'usage des cliniciens et des chercheurs et annex	2010	France
20	Nuffield Council on Bioethics	Human bodies: Donation for medicine and research	2011	UK
21	Secretary's Advisory Committee on Genetics, Health and Society	Policy Issues Associated with Undertaking A New Large U.S. Population Cohort Study of Genes, Environment, and Disease	2007	US
22	Expert Group on a National Cancer Biobank	Recommendations for the Establishment of a National Cancer Biobank	2008	Ireland
23	National Health and Medical Research Council	Biobanks Information Paper	2010	Australia
24	Confederation of Cancer Biobanks	Human Research Tissue Banks / Resources / Biobanks: Guiding Principles	2012	UK
25	House of Lords' Select Committee on Science and Technology	Fourth Report: Human Genetic Databases: Challenges and Opportunities	2001	UK
26	National Dialogue on Cancer	National Biospecimen Network Blueprint	2003	UK
27	National Cancer Research Institute, National Cancer Intelligence Network and onCore UK	Samples and Data for Research: Template for Access Policy Development	2009	UK

	International biobank networks	Document title	Date of publication	Country
1	ADDGENE	ADDGene MTA	Online	International
2	International Cancer Genome Consortium	Consortium Policy and Guidelines	Online	International
3	International Childhood Cancer Cohort Consortium	International Childhood Cancer Cohort Consortium Policies and Procedures Manual	2007	International
4	European Network of DNA, Cell and Tissue Banks for Rare Diseases	MTA + Network Charter + Outstanding legal and ethical issues on biobanks	2006	International
5	GenomEUtwin	Data Access and Security Policy + Biological Sample Transfer Agreement (STA)	2007	International
6	Genetics of Healthy Aging	*No information publicly available*	N.A.	International
7	Colon Cancer Family Registries	Colon-CFR Application and review process	Online	International

	European biobank networks	Document title	Date of publication	Country
8	TubaFrost	D.7.1. Code of Conduct for the residual use of tissue for research + online access rules + D.6.1. assessment of policies and rules for a networked tissue bank + TubaFrost Tissue Transfer Agreement + D. 6.2. Policy and rules for monitoring and use of banked tissues in research + Milestone 6.1: Report policy and rules for contribution to and use of banked tumor tissue in research	2003 & 2004	EU
bis	EurocanPlatform biobanking	*Under development*	N.A.	EU
9	BBMRI.EU	Data Access Agreement + Partner Character	2010	EU

	European biobank networks (continued)	Document title	Date of publication	Country
10	EORTC	POL008: Release of data from EORTC studies for use in External Research Projects + POL009: Disclosure of Results and Publication Policy + POL016: Protocol Development Process, Selection and Approval Procedures for EORTC Studies + POL020: Human Biological Material Collection, Storage and Use	2011	EU
11	NUGO	Bioethic guidelines on Human Studies	2007	EU
12	EUSTAR	EUSTAR biobanking: Recommendations for the collection, storage and distribution of biospecimens in scleroderma research	2008	EU
13	CRIP	CRIP Rules for Access + Access to the CRIP Database – Application	2010	EU
14	IMPACTS / Pan-European Network of archive tissue biobanks	*No information publicly available*	N.A.	EU
15	BrainNet Europe	Information requested from Applicant for Tissue from BNE + Declaration of tissue use	No date	EU
16	Alliance against Sudden Cardiac Death	*No information publicly available*	N.A.	EU

	National biobank networks	Document title	Date of publication	Country
17	String of Pearls Initiative	Framework regulation	2009	the Netherlands
18	Center for Medical Innovation	Ethical and Legal Framework Flemish Biobanks	2012	Belgium
19	Réseau des biobanques de Wallonie / Fédération Wallonie-Bruxelles	*Under development*	N.A.	Belgium
20	Belgian Virtual Tumourbank	BVT Sample access policy	2013	Belgium
21	Swedish Large-Scale Biobank of BBRMI.se	*No information publicly available in English*	N.A.	Sweden
22	Italian Network of Research Biobanks	*No information publicly available*	N.A.	Italy
23	Wellcome Trust-Case Control Consortium	Guidelines and Information + Application form + Data Access Agreement	2009 & 2010	UK
24	Network of Centers of Excellence of Canada	Confidential Information and Material Transfer Agreement	No date	Canada
25	SAGE bionetworks	Terms of Use + Sage Bionetworks Data Sharing Governance	Online	US
26	Cohort of Norway	Guidelines for access to CONOR materials	2004	Norway
27	National Biobanks of Finland	*No information publicly available*	N.A.	Finland
28	Generation Scotland	(Draft) Management, Access and Publications Policy + Data/Material Transfer Agreement	2011	Scotland
29	the Netherlands Brain Bank	Online tissue application information + leaflet "information for tissue applicants" + MTA	Online	the Netherlands
30	Canadian Tumor Repository Network	CTRNet Policy Ethics + Policy Material Release + Policy Privacy and Security + SOP Material Request and Release	2008 & 2009	Canada
31	CNIO Tumor Bank Network	Description on website how to obtain tissue + application form	Online	Spain
32	Canadian Partnership for Tomorrow project	CPTP Data Access Policy	2011	Canada
33	Banca Biologica CNESPS	*No information publicly available*	N.A.	Spain
34	National Heart, Lung, and Blood Institute Cohort Studies	Operational guidelines	2010	US
35	Swedish Twin Registry	Swedish Twin Registry Policy Statement Regarding Collaboration	2007	Sweden

	National biobank networks (continued)	Document title	Date of publication	Country
36	Instituto de Investigacion de Enfermedades Rares	Webpage 'Solicitud Lineas Celulares': http://www.isciii.es/htdocs/terapia/terapia_solicitudLineasCelulares.jsp	Online	Spain
37	Pediatric Rheumatology Tissue Repository	*No information publicly available*	N.A.	US
38	Cooperative Human Tissue Network	CHTN Application	2011	US
39	Early Detection Research Network	*No information publicly available*	N.A.	US
40	Cancer Research Network of the FRSQ	Biological Material and Data Request Form + Commitment to confidentiality + UBMTA implementing letter	2007	Canada
41	Tissue Bank of the Respiratory Health Network of the FRSQ	Description de la demande + Contrat d'utilisation pour l'investigateur + Autorisation de se procurer le matériel humain	Online	Canada
42	Telethon Network of Genetic Biobanks	Charter and Guidelines	2004	Italy
43	Biobank Ireland trust	*Under development*	N.A.	Ireland
44	Ciberes Spanish Respiratory Research Network	Terms of use	2010	Spain
45	Italian Biobank Network	*No information publicly available*	N.A.	Italy
46	Network of German Biobanks	Application Form	Online	Germany
47	Red de Biobancos Oncologicos de la Comunidad Valenciana	MTA	No date	Spain
48	Rete Italiana Biobanche Per L'Oncologia	*No information publicly available*	N.A.	Italy
49	Stiftung Biobank Suisse	User Guide for Researchers	2011	Switzerland
50	Tumorothèques du cancéropole PACA	*No information publicly available*	N.A.	France
51	Biobanques	*Under development*	N.A.	France

	International biobanks	Document title	Date of publication	Country
1	IARC, WHO	IARC Policy on Access to Human Biological Materials + MTA (with in Annex General Conditions)	2013	International

	European biobanks	Document title	Date of publication	Country
2	European Searchable Tumour Line Database	Order form on webpage: http://www.medizin.uni-tuebingen.de/estdab/	Online	EU

	National biobanks	Document title	Date of publication	Country
3	UK Biobank	Access procedure	2011	UK
bis	UK Biobank EGC	UK Biobank Ethics and Governance Framework	2007	UK
4	Karolinska Institutet Biobank	(Standard) Material Transfer Agreement + Sample withdrawal Order	2011	Sweden
5	Integrated Biobank of Luxembourg	*None*	N.A.	Luxembourg
6	Banco Nacional de ADN	Conditions of use and researchers commitments	Online	Spain
7	Norwegian Mother and Child Cohort Study	The Norwegian Mother and Child Cohort Terms and Conditions for access to data and biological materials	2010	Norway

	National biobanks (continued)	Document title	Date of publication	Country
8	Koragen	Project Agreement of Data and/or Biosamples Transfer	2010	Germany
9	Centre National de la Recherche	Modèle Accord de transfer de matériel	2010	France
10	CARTaGENE	Uniform access agreement (+ Samples and Access and Use Policy for Data and Samples(/Data Access Policy))	2009	Canada
11	National PKU biobank	Article in scientific journal: 'storage policies and use of the Danish Newborn Screening Biobank'	2007	Denmark
12	Estonian Biobank	Data Release + Application form for Data Release	No date	Estonia
13	UK DNA Banking Network	Article in scientific journal: UK DNA banking network: a “fair access biobank”	2009	UK
14	LifeLines Cohort & Biobank initiative	Guidelines for access to LifeLines data	2009	the Netherlands
15	EuroBoNet Biobank	*No information publicly available*	N.A.	the Netherlands
16	Genome Database of Latvian Population	Material Transfer Agreement	No date	Latvia
17	Généthon DNA and Cell Bank	DNA and Cell Bank Charter	2006	France
18	British Columbia Cancer Agency Tumour Repository	Materials Access Application Form + MTA	No date	Canada
19	LifeGene	Access and IP Policy	2011	Sweden
20	Manchester Cancer Research Center	MCRC Biobank Access Policy	2010	UK
21	HIV HGM Spanish Biobank	Release agreement + Procedure: 'Establishment of an Agreement for the release of samples'	2008	Spain
22	National Center for Tumor Diseases Heidelberg	Information on website + information from interview	Online	Germany

Legend: The information found in the above listed documents was supplemented with information found on the websites of the concerned biobank initiatives
The 'column date of publication' mentions 'no date', when the access arrangements did not specify the data of
The column 'date of publication' mentions 'online', when the access arrangements was accessed online and no publication date was indicated

Annex 2: Supplementary Table to Chapter 1: Overview of qualitative results of comparative analysis

Table 9: Results of comparative analysis of access arrangements

Geographical scope	Organizations	Network	Biobank
International	6	7	1
Regional	2	9	1
National	19	35	20
Total	27	51	22

Note: This geographical overview contains both the publicly available and unavailable access arrangements

Publicly available	Yes	Unavailable	Under development	None
Organizations	26			1
Biobank networks	36	12	3	
Biobanks	20	1		1

Condition 1: Access to data and/or HBM	Organizations	Networks	Biobanks
Data	2	5	0
HBM	0	5	5
Both	23	26	15
Not specified	1	0	0

Condition 2: Type of HBM	Organizations	Networks	Biobanks
All HBM	12	10	6
Genetic HBM and other tissue	0	3	2
Only genetic HBM	1	5	5
Body fluids and other tissue	2	0	1
Only other tissue	0	10	6
Only body fluids	0	0	0
Not specified	8	3	0
No access to HBM	2	5	0

Condition 3: Data type	Organizations	Networks	Biobanks
All data	12	8	1
Genetic and other health data	1	3	2
Only genetic data	4	9	7
Only other (health) data	0	8	3
Other (health) data and epidemiologic data	0	0	1
Only epidemiologic data	0	0	0
Not specified	8	3	1
No access to data	0	5	4

Condition 4 & 5: Level of ownership of primary HBM and data	Organizations		Networks		Biobanks	
	HBM	Data	HBM	Data	HBM	Data
Biobank network and biobank	0	1	1	1	0	0
Only biobank network	0	0	1	3	0	0
Only biobank	4	2	6	6	7	6
Only PI	0	0	0	0	0	0
Exclude at all levels	6	8	1	0	0	0
Not specified	14	15	22	23	13	10

Condition 6 & 7: Level of custodianship of HBM and data	Organizations		Networks		Biobanks	
	HBM	Data	HBM	Data	HBM	Data
Biobank network and biobank	1	1	4	4	0	0
Only biobank network	2	2	6	10	0	0
Only biobank	3	3	15	11	14	11
Biobank, funder and PI	1	1	0	0	0	0
Biobank, funder and PI	1	1	0	0	1	1
Biobank and funder	1	1	0	0	0	0
Only PI	1	1	0	0	1	0
Not PI	3	3	1	1	0	0
Only funder	0	0	0	0	0	0
Not specified	11	16	6	6	4	3

Condition 8: Access committees	Organizations	Networks	Biobanks
Yes	14	23	14
No	1	1	0
Not specified	11	12	6

Condition 9: Mandata access committee	Organizations	Networks	Biobanks
Decide on each request	7	13	12
Decide on each request and policy	4	3	0
Decide only on particular requests	0	0	1
Decide on particular requests and policy	0	1	0
Decide only on (general) policy	0	1	0
Not specified	3	5	1

Condition 10: Screening of scientific merit	Organizations	Networks	Biobanks
Yes	11	18	11
Extensive	8	0	4
Limited to check of formalities	0	3	0
None	1	0	0
Not specified	14	18	9

Condition 11: Access by industrial company	Organizations	Networks	Biobanks
No (commercial) use by industrial companies	1	5	7
Commercial use	7	4	1
Unspecified use by industrial company	5	7	6
Only with prior written approval	4	4	2
Not specified	9	16	4

Condition 12 & 13: External/industrial applications: Different legal conditions and fees	Organizations		Networks		Biobanks	
	Conditions	Fees	Conditions	Fees	Conditions	Fees
Yes	3	4	7	3	2	4
No	4	2	1	2	4	3
Not specified	9	10	7	10	3	2
Not applicable	9	9	16	16	4	4

Condition 14: Priority setting	Organizations	Networks	Biobanks
Yes (total)	6	8	8
Precedence	1	0	2
Collector	2	2	0
Scientific merit	4	3	3
Funding	1	0	0
Working in particular institution	2	1	0
Internal/affiliated project	2	5	2
Lottery	1	0	0
Linking of other sources with BB	0	1	0
Increasing quality of sources of BB	0	1	0
Closeness to purpose of BB	0	3	4
Required number of HBM	0	1	3
Technical requirements	0	0	1
Geographical closeness	0	3	0
Peer review funded	0	1	0
Not specified	20	28	12

Condition 15: Intellectual property	Organizations	Networks	Biobanks
IP on primary HBM	2	1	4
No IP on primary HBM	7	3	3
No reach-through IP for biobank	7	7	5
Reach-through IP for biobank	0	0	3
Research use license	1	2	3
Not specified	14	25	9

Condition 16: Exclusive (access) right of applicant	Organizations	Networks	Biobanks
Yes	3	4	5
No	1	4	3
Only to derived data	1	0	0
Not specified	21	28	12
Condition 17: Preferential (access) right of collector	**Organizations**	**Networks**	**Biobanks**
Yes	7	4	4
No	1	1	2
Not specified	18	31	14

Condition 18: Benefit sharing	Organizations	Networks	Biobanks
Yes	16	2	0
Recognition/feedback to donors	2	0	0
Contribution to BB	1	1	0
Contribution to public fund	0	1	0
Preferential access to healthcare developments	3	0	0
No	0	0	0
Not specified	10	34	20

Condition 19: Sharing and/or return of data/results	Organizations	Networks	Biobanks
Yes	14	17	15
No	0	0	0
Not specified	12	19	5

Condition 20: Data protection	Organizations	Networks	Biobanks
Coded	1	6	4
Anonymised	0	4	2
Coded or anonymised	4	7	4
Identifiable	0	0	0
All	2	2	0
Not specified	19	17	10

Condition 21: Return and/or destruction of tissue	Organizations	Networks	Biobanks
Yes	13	17	12
No	1	0	0
Not stipulated	12	19	8

Note: In some cases, access arrangements contained several possible answers to the questions posed. That is why the number of answers might be higher than the number of access arrangements that we reviewed.

Annex 3: Interview guide for semi-structured interviews

1. Factual biography
   1.1. Interview date
   1.2. Name of informant
   1.3. Position of informant
   1.4. Short description of the relationship of the informant with biobanking
2. Short description of purpose and nature of the interview
   - The current research would like to study **practical experience** and **personal opinion on hopes and concerns** regarding the relationship between custodians and researchers/PI
3. Guidelines
   - The informant's identity remains anonymous in the written report of the study and responses are treated in confidence. There will only be references to the concerned biobank or function, but not the combination of both, since this would allow identification of the informant
   - Request permission to tape record interview
4. Checklist of topics
   4.1. Aim of research project:
      i. Collect data on **practical experience** and **personal opinion on hopes and concerns** in collaboration between custodian and researcher
   4.2. Questions in relation to access to biobanks:
      1. Professional experience with biobanking?
         a. How is your institute involved in biobanking?
      2. How to handle requests for access?
         a. Policy at your institute? Rules in your country?
         b. Your experience? Your own opinion?
         c. Is access policy/arrangement publicly available?
      3. Distinction between access to HBM and access to data?
         a. Different policy?
      4. Leftover HBM?
         a. Policy at your institute? Rules in your country?
         b. Your experience? Your own opinion?
      5. Which benefits?
      - Prompts: Participation in such benefits? When?
         - Policy at your institute? Rules in your country?

- Your experience? Your own opinion?

6. What is understood by returning 'research results'

- Is 'Returning research results' a category of benefits?
  - Policy at your institute? Rules in your country?
  - Your experience? Your own opinion?
  - Decision of researcher on use of returned results?
    - What if HBM was prospectively collected at the request of the applicant?

7. Publicly available information on access to HBM and/or associated data?

- Prompts: How to increase transparency?
  - Policy at your institute? Rules in your country?
  - Your experience? Your own opinion?
- Registration obligation?

8. Access by industry: Allow access to biobanks? Different policy?

4.3. Open question: Any other hopes or concerns in relation to access to biobanks?

5. Closing comments
   5.1. Debriefing
   5.2. Copy of final report will be sent

Annex 4: Common list of concepts

Aggregated dimensions	2nd order themes	1st order concepts
1. Strategy	Partnership/collaboration	
2. Access requests	2.1 Decision body	Funding body Sample access committee
	2.2 Decision criteria	HBM from rare diseases or rare HBM Scientific value/merit: Research questions Quality of research (study design, scientific validity, statistical relevance) Societal or medical relevance/benefit Commercial or not Approval by ethics committee or other body Research experience/merit Other criteria Correspondence with vision
	2.3 Extent of detail	Abstract or complete protocol Amount and type of HBM and type of patients required Research hypothesis/objective Statistical relevance of sample size Other Research method/technique
3. Return and/or destruction of left-over HBM	3.1 Criteria for return	Prior agreement Rare vs. common HBM Other Quality of returned HBM/reusability
	3.2 Criteria for destruction	Complexity Cost
	3.3 Criteria for re-use	Amendment/Full review
	3.4 Alternatives	Providing limited number/sharing in parts
4. Participation in benefits	4.1 Criteria for benefit sharing	(scientific)contribution/inventive step Other Collaboration (agreement)
	4.2 Mechanism of benefit sharing	Sharing of IP/royalty/upfront payment Public contribution fee/central funding Other User fee/cost recovery
5. Return, sharing and publication of research results	5.1 Advantage of return	Avoid duplication and unnecessary costs Enrich collection Share scientific knowledge Quality control Reinterprete data with new expertise
	5.2 Criteria for return	Quality and reusability of results Infrastructure/storage capacity Respect interest researcher Other Protection of personal integrity
	5.3 Criteria for not return	Difficulty to interprete Competitive advantage
	5.4 Obligatory or not	Requirement for access (to additional data)
	5.5 Type of data/HBM	Negative results/validated results/raw data Modified HBM
	5.6 Power to decide	Suggestion/obligation to collaborate Decision to share reseach results

Aggregated dimensions	2nd order themes	1st order concepts
6. Initiative for collection	6.1 Initiative biobank	Use for research specified in request Single 'delivery' fee More rights for biobank
	6.2. Initiative collector	(transfer of) Decision (right) to use HBM for project Fee for services/entire concept Priority right to use/publish
7. Exclusive access	7.1 Why not?	
	7.2 Alternative concepts	Priority right/preferential access
8. Publicly available information	8.1 Which information	Line of research Commercial non sensitive information Abstract
	8.2 Advantage	Avoid duplication; Enable synergies/collaborations; Knowledge about existing research/failures

Annex 5: Web of rights and obligations of custodian and applicant

1. Rights and obligations in relation to decision on access to HBM and data

A. Rights of custodian

- Evaluate access request and decide on access to HBM
- Consensus:
- Evaluate availability and suitability of HBM and data for project
- Evaluate impact on existing collection of HBM and data
- Determine priorities between different research projects
- No consensus:
  - Evaluate quality and scientific and medical useful of project
  - Evaluate research merits of applicant
  - Evaluate ethical value

B. Obligations of custodians

- Consensus:
- Access committee should dispose of sufficient expertise/experience
- Access committee should act independently
- No consensus: Should access committee
- follow advice of ethics committee?
- consult external experts?
- motivate its decisions?
- have discretionary power or apply criteria determined by national legislator?

C. Rights of applicant

- Access collection of HBM and data
- Use HBM and data in research project
- Keep certain information confidential
- Priority access in case applicant collected HBM and data

D. Obligations of applicant

- Consensus:
- Use for specific project and certain time period
- Provide synopsis of project
- No consensus:
- Provide elaborated description of project
- Specify type of research
- Provide technical motivation of requested HBM and data

2. Rights and obligations in relation to leftover HBM

A. Rights of custodian

- Decide on return or destruction
- Decide on use in new or follow-up project
- Verify leftover HBM

- Provide minimum amount of HBM

B. Obligations of applicant
- Inform biobank about leftover HBM
- Return or destroy
- Submit new request for new use of HBM
- Prohibition to transfer to third party

3. Right to participate in benefits of research project

A. Rights of custodian
- Charge access fee
  - Right to distinguish between internal applicant and external and industrial applicants
- Request that some of the benefits are fed back into biobank infrastructure
- Share in benefits of research project
  - Condition: Scientific contribution to project

B. Right of applicant
- Enjoy benefits of research project

C. Obligations of applicant
  - Pay access fee
  - Feed some of the benefits back into biobank infrastructure

4. Right to request the return of research results

A. Rights of custodian
- Request return and sharing of research results
- Conditions
  - Consensus:
    - Proper infrastructure to store and share research results
    - Clear rules on access to research results
    - Sufficient recognition of researcher that generates results
    - Respect legitimate interest of researcher that generates results
- No consensus
  - Obligatory requirement to access collection of HBM and data

B. Rights of applicant
- Be informed and/or consulted on access to research results
- Sufficient recognition for returning research results
- Respect his legitimate interests

Professional career

1 Professional career

- September 2012 until June 2013 and January until July 2014: Visiting Researcher at Copenhagen University
- September 2010 until March 2015: PhD Candidate at KU Leuven
- October 2005 until March 2011: Attorney at Law at Stibbe Brussels
- February 2005 until October 2005: Scientific Researcher at VUB

2 List of original peer-reviewed publications

1. Articles (IT or AT) indexed in VABB

   - Verlinden Michiel, Nys Herman, Ectors Nadine and Huys Isabelle, Access to biobanks: harmonization across biobank initiatives. Biopreserv Biobank. 2014; 12(6): 415–22.
   - Stevens Hilde, Verbeken Gilbert, Verlinden Michiel, Huys Isabelle (2011). Kijken naar cel- en gentherapie als „geneesmiddel" – Technische en juridische uitdagingen in ATMP-ontwikkeling. *Tijdschrift voor Geneeskunde, 67* (22), 1105-1111 (VABB-1).
   - Verlinden Michiel, Stevens Hilde, Huys Isabelle (2011). Geen octrooibescherming van genetische informatie bij functieverandering via verwerking in een biotechnologisch proces. *Intellectuele Rechten - Droits Intellectuels, 3*, 213-216 (VABB-1).

2. Articles IT not indexed in WoS or VABB

   - Pirnay, Jean-Paul; Baudoux, Etienne; Cornu, Olivier; Delforge, Alain; Delloye, Christian; Guns, Johan; Heinen, Ernst; Van den Abbeel, Etienne; Vanderkelen, Alain; Van Geyt, Caroline; van Riet, Ivan; Verbeken, Gilbert; De Sutter, Petra; Verlinden, Michiel; Huys, Isabelle; Cockbain, Julian; Chabannon, Christian; Dierickx, Kris; Schotsmans, Paul; De Vos, Daniel; Rose, Thomas; Jennes, Serge and Sterckx, Sigrid, "Access to human tissues for research and product development: From EU regulation to alarming legal developments in Belgium", EMBO reports 2015 (accepted for publication)
   - Callewaert Koen *, Clerix Andre*, D'Halleweyn Nele*, Dauwe Brigitte*, De Gryse Erik*, Dekoninck Christian *, Ronse Christoph*, Theunis Patrick*, Verlinden Michiel* (2010). [AIPII - Question Q204P] Liability for contributory infringement of IPRs [Intellectual property rights] - certain aspects of patent infringement. *Revue de Droit Intellectuel: l'Ingénieur-Conseil, 3*, 317-325.
   - Dupont Renaud*, Kaesmacher Dominique*, Santantonio Olivia*, Sorreaux Gregory*, Van den Bulck Paul*, Verlinden Michiel*, Vernimme Ignace* (2009). AIPPI Report on Q210: The Protection of Major Sports Events and associated Commercial activities through Trademarks and other IPR. *Revue de Droit Intellectuel: l'Ingénieur-Conseil*, 258.
   - Wright David, Friedewald Michael, Schreurs Wim, Verlinden Michiel, Gutwirth Serge, Punie Yves, Maghiros I, Vildjiounaite E, Alahuhta P (2008). The Illusion of Security: A fiction scenario of daily life. *Communications of the ACM, 51* (3), 57-63 (IF publication year: 2.65) (IF most recent: 2.86).

- Cornu Emmanuel *, De Gryse Ludovic*, Kaesmacher Dominique*, Leherte George*, Meyer Gunther*, Missoten Stephanie*, Mottet Annick*, Santantonio Olivia*, Van Bunnen Louis*, Verlinden Michiel* (2008). L'épuisement des droits de propriété intellectuelle dans les cas de recyclage et de réparation des produits. *Revue de Droit Intellectuel: l'Ingénieur-Conseil, 3*, 365-385.
- Verlinden Michiel, Vernimme Ignace (2008). IP-aandachtspunten in het kader van een due diligence. *Intellectuele Rechten - Droits Intellectuels, 4*, 331-338.

3. Book IBa not indexed in VABB

- Ahonen, P., Alahuhti, P., Daskala, B., Delaitre, S., De Hert, P., Friedewald, M., Gutwirth, S., Lindner, R., Maghiros, I., Moscibroda, Punie, Y., Schreurs, W., Verlinden, M., Vildjionaite, E., Wright, D. (2008). *Safeguards in a World of Ambient Intelligence (SWAMI), Spring Science + Business Media B.V. 2008, 290 p.* (Friedewald, Michaël, Ed. Gutwirth, Serge, Ed. Wright, David, Ed. Vildjiounaite, Elena, Ed. Punie, Yves, Ed.). The International Library of Ethics, Law and Technology, 1. Spring Science + Business Media B.V.

4. Book ABa-p (other: no VABB type)

- Meyer, G., Verlinden, M., Vandewynckel, S. (2013). *Overzicht van procesregels inzake Intellectuele Eigendomsrechten.* Brussels: UGA.

3 Presentations at conferences and published abstracts

1. Presentation at conferences

- Poster Presentation ‘Access rules stimulating the exchange of human biological material within biobank networks’ at 3rd European Conference on Health Law on 6-7 October 2011 in Leuven
- Poster and Oral Presentation ‘Access rules within biobank networks’ at ESBB Inaugural Conference on 16-19 November 2011 in Marseille
- Oral Presentation ‘Comparative analysis of access instruments’ at Biobanking Network Meeting on 24 August 2011 in Leuven
- Poster Presentation ‘Comparative analysis of access instruments’ at HandsOn: Biobanks 2012 on 20-21 September 2012 in Uppsala
- Poster presentation ‘Comparative analysis of access instruments’ at Joint Congress of ESBB & the Spanish National Biobank Network on 7-9 November 2012 in Granada
- Oral Presentation ‘Access to human biological material and data stored in (research) biobanks’ at Colloque ‘Les Biobanques’ on 17 April 2013 in Brussels
- Poster Presentation ‘Balancing the rights and obligations of stakeholders in relation to access to biobanks’ at ESBB Conference 2013 on 8-11 November 2013 in Verona
- Poster Presentation ‘Lack of clear and harmonized information on key access principles’ at HandsOn 2013 on 21-22 November 2013 in Den Hague

- Poster and Oral Presentation 'Access to biobanks: relationship between custodian and applicant' at ESBB Conference 2014 on 22-24 October 2014 in Leipzig
- Oral Presentation 'Access to biobanks: relationship between custodian and applicant' at Workshop "Driving Regenerative Medicine to the Market and Clinic: An Exploration of Enablers, Impediments, and Ethical-Legal Challenges" on 4-6 November 2014 in Toronto

2. Conference Abstracts

- Verlinden, M., Ectors, N., Nys, H., Huys, I. (2012). Legal Nature of Custodianship of Human Biological Material Stored in Biobanks. *Biopreservation and Biobanking: Vol. 10* (5). ESBB & Spanish National Biobank Network Joint Conference. Granada, 7-9 November 2012 (pp. A39-A39).
- Verlinden, M., Ectors, N., Nys, H., Huys, I. (2011). Access Rules within Biobank Networks. *Biopreservation and Biobanking: Vol. 9* (3). ESBB's Inaugural Conference. Marseille, 16-19 November 2011 (pp. 304-304).